TREATMENT FOR ALZHEIMER'S DISEASE AND RELATED CONDITIONS

This invention relates to methods and materials for use in therapeutic treatment of the human body. In particular, it provides methods of treating diseases associated with the deposition of β-amyloid peptide in the brain, such as Alzheimer's disease, or of preventing or delaying the onset of dementia associated with such diseases.

Alzheimer's disease (AD) is the most prevalent form of dementia. Its diagnosis is described in the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} ed., published by the American Psychiatric Association (DSM-IV). It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and general cognitive function, and pathologically characterized by the deposition of extracellular proteinaceous plaques in the cortical and associative brain regions of sufferers. These plaques mainly comprise fibrillar aggregates of β-amyloid peptide (Aβ). Aβ is formed from amyloid precursor protein (APP) via separate intracellular proteolytic events involving the enzymes β-secretase and γ-secretase. Variability in the site of the proteolysis mediated by γ-secretase results in Aβ of varying chain length, e.g. Aβ(1-38), Aβ(1-40) and Aβ(1-42). N-terminal truncations such as Aβ(4-42) are also found in the brain, possibly as a result of variability in the site of proteolysis mediated by β-secretase. For the sake of convenience, expressions such as "Aβ(1-40)" and "Aβ(1-42)" as used herein are inclusive of such N-terminal truncated variants. After secretion into the extracellular medium, the initially-soluble Aβ forms aggregates which ultimately result in the insoluble deposits and dense neuritic plaques which are the pathological characteristics of AD.

Other dementing conditions associated with deposition of Aβ in the brain include cerebral amyloid angiopathy, hereditary cerebral haemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

Various interventions in the plaque-forming process have been proposed as therapeutic treatments for AD (see, for example, Hardy and Selkoe, *Science*, 297 (2002), 353-6). One such method of treatment that has been proposed is that of

blocking or attenuating the production of Aβ for example by inhibition of β- or γ-secretase. It has also been reported that inhibition of glycogen synthase kinase-3 (GSK-3), in particular inhibition of GSK-3α, can block the production of Aβ (see Phiel et al, *Nature*, **423** (2003), 435-9).

Other proposed methods of treatment include administering a compound which blocks the aggregation of Aβ, and administering an antibody which selectively binds to Aβ.

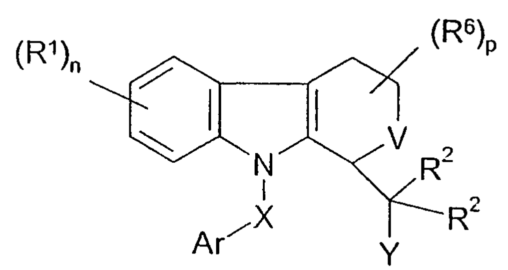
An alternative mode of treatment is that of modulation of the action of γ-secretase so as to selectively attenuate the production of Aβ(1-42). This results in preferential secretion of the shorter chain isoforms of Aβ, which are believed to have a reduced propensity for self-aggregation and plaque formation, and hence are more easily cleared from the brain, and/or are less neurotoxic. Compounds showing this effect include certain non-steroidal antiinflammatory drugs (NSAIDs) and their analogues (see WO 01/78721 and US 2002/0128319 and Weggen et al *Nature*, **414** (2001) 212-16; Morihara et al, *J. Neurochem.*, **83** (2002), 1009-12; and Takahashi et al, *J. Biol. Chem.*, **278** (2003), 18644-70). Compounds which modulate the activity of PPARα and/or PPARδ are also reported to have the effect of lowering Aβ(1-42) (WO 02/100836). NSAID derivatives capable of releasing nitric oxide have been reported to show improved anti-neuroinflammatory effects and/or to reduce intracerebral Aβ deposition in animal models (WO 02/092072; Jantzen et al, *J. Neuroscience*, **22** (2002), 226-54).

EP 0234708, EP 0307077 and EP 0300676 disclose tetrahydrocarbazole 1-alkanoic acids which act as prostaglandin and thromboxane antagonists and are said to be useful in treating asthma, diarrhea, hypertension, angina, platelet aggregation, cerebral spasm, premature labour, spontaneous abortion and dysmenorrhea, as cytoprotective agents, and in limiting cyclosporine-induced nephrotoxicity. There is no disclosure or suggestion of any effect on the secretion of Aβ, or of any utility in the treatment or prevention of AD or any other disorders associated with deposition of Aβ in the brain.

WO 01/79169, WO 02/08186 and WO 03/062200 disclose various cycloalkano-indoles as prostaglandin receptor antagonists, but again there is no disclosure of utility in treating AD or related disorders.

It has now been found that certain tetrahydrocarbazole 1-alkanoic acids and related compounds have the desirable property of selectively inhibiting production of Aβ(1-42).

According to the present invention there is provided the use, for the manufacture of a medicament for treatment or prevention of a disease associated with the deposition of β-amyloid in the brain, of a compound of formula I:



I

wherein V represents a bond, CH_2 or CH_2CH_2;

X represents SO_2 or CHR^3 where R^3 is H or a hydrocarbon group containing up to 10 carbon atoms which is optionally substituted with halogen, CF_3, C_{1-4}alkoxy or C_{1-4}alkylthio;

Y represents CO_2H or tetrazole;

Ar represents phenyl which optionally bears up to 3 substituents independently selected from hydrocarbon groups of up to 6 carbon atoms and $(CH_2)_m$-Z where m is 0, 1 or 2 and Z represents halogen, N_3, CN, CF_3, OCF_3, OR^4, $S(O)_tR^4$ where t is 0, 1 or 2, CO_2R^4, tetrazole, $N(R^4)_2$, $NHCOR^5$, $NHCON(R^4)_2$, $CON(R^4)_2$, $SO_2N(R^4)_2$, $NHSO_2R^5$, COR^5, or $OCOR^5$;

n is 0, 1, 2 or 3;

each R^1 is independently selected from nonaromatic hydrocarbon groups of up to 6 carbon atoms and $(CH_2)_q$-W where q is 0, 1 or 2 and W represents halogen, CN, CF_3, OR^4, $N(R^4)_2$, $S(O)_tR^4$ where t is 0, 1 or 2, CO_2R^4, tetrazole, $CON(R^4)_2$, $SO_2N(R^4)_2$, COR^5, $OCOR^5$ or phenyl or heteroaryl either of which optionally bears up

to 3 substituents selected from halogen, CF_3, OCF_3, CN, OH, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio or C_{1-4}alkoxycarbonyl;

each R^2 is independently H or C_{1-4}alkyl; or one R^2 group together with an R^6 group attached at the same ring position as the $-C(R^2)_2$-Y moiety completes a spiro-linked hydrocarbon ring of 3-6 members;

R^4 represents H or a hydrocarbon group of up to 7 carbon atoms, optionally substituted with halogen, CN, CF_3, OH, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl; or two R^4 groups attached to the same nitrogen atom may complete a 5- or 6-membered heterocyclic ring;

R^5 represents R^4 that is other than H;

p is 0, 1 or 2; and

R^6 represents C_{1-6}alkyl, C_{2-6}alkenyl or phenyl, benzyl or heteroaryl, said phenyl, benzyl or heteroaryl optionally bearing up to 3 substituents selected from halogen, CN, CF_3, OCF_3, OR^4, CO_2R^4, COR^5, $OCOR^5$ and C_{1-4}alkyl; or an R^6 group together with an R^2 group may complete a spiro-linked hydrocarbon ring as defined previously;

or a pharmaceutically acceptable salt thereof.

In a particular embodiment of the invention, each R^2 is independently H or C_{1-4}alkyl.

In a sub-embodiment, V represents CH_2;

X represents SO_2 or CHR^3 where R^3 is H or C_{1-6}alkyl;

Ar represents phenyl which optionally bears up to 3 substituents independently selected from nonaromatic hydrocarbon groups of up to 6 carbon atoms and $(CH_2)_m$-Z where m is 0, 1 or 2 and Z represents halogen, N_3, CN, CF_3, OR^4, $S(O)_tR^4$ where t is 0, 1 or 2, CO_2R^4, tetrazole, $N(R^4)_2$, $NHCOR^5$, $NHCON(R^4)_2$, $CON(R^4)_2$, $SO_2N(R^4)_2$, $NHSO_2R^5$, COR^5, or $OCOR^5$;

each R^1 is independently selected from nonaromatic hydrocarbon groups of up to 6 carbon atoms and $(CH_2)_q$-W where q is 0, 1 or 2 and W represents halogen, CN, CF_3, OR^4, $S(O)_tR^4$ where t is 0, 1 or 2, CO_2R^4, tetrazole, $CON(R^4)_2$, $SO_2N(R^4)_2$, COR^5, $OCOR^5$ or phenyl which is optionally substituted with halogen, CF_3, CN, OH, C_{1-4}alkyl, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl;

R^4 represents H or a hydrocarbon group of up to 7 carbon atoms, optionally substituted with halogen, CN, CF_3, OH, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl;

R^6 represents C_{1-6}alkyl, C_{2-6}alkenyl or phenyl or benzyl, said phenyl or benzyl optionally bearing up to 3 substituents selected from halogen, CN, CF_3, OR^4, CO_2R^4, COR^5, $OCOR^5$ and C_{1-4}alkyl;

and Y, n, R^2, R^5 and p are as defined previously.

The disease associated with deposition of Aβ in the brain is typically Alzheimer's disease (AD), cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome, preferably AD.

In a second aspect, the invention provides the use of a compound of Formula I as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating, preventing or delaying the onset of dementia associated with Alzheimer's disease, cerebral amyloid angiopathy, HCHWA-D, multi-infarct dementia, dementia pugilistica or Down syndrome.

The invention also provides a method of treating or preventing a disease associated with deposition of Aβ in the brain comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I as defined above or a pharmaceutically acceptable salt thereof.

In a further aspect, the invention provides a method of treating, preventing or delaying the onset of dementia associated with Alzheimer's disease, cerebral amyloid angiopathy, HCHWA-D, multi-infarct dementia, dementia pugilistica or Down syndrome comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I as defined above or a pharmaceutically acceptable salt thereof.

The compounds of Formula I modulate the action of γ-secretase so as to selectively attenuate production of the (1-42) isoform of Aβ without significantly lowering production of the shorter chain isoforms such as Aβ(1-40). This results in secretion of Aβ which has less tendency to self-aggregate and form insoluble deposits, is more easily cleared from the brain, and/or is less neurotoxic. Therefore, a further aspect of the invention provides a method for retarding, arresting or preventing the accumulation of Aβ in the brain comprising administering to a subject in need thereof

a therapeutically effective amount of a compound of Formula I as defined above or a pharmaceutically acceptable salt thereof.

Because the compounds of formula I modulate the activity of γ-secretase, as opposed to suppressing said activity, it is believed that the therapeutic benefits described above will be obtained with a reduced risk of side effects, e.g. those that might arise from a disruption of other activities mediated by γ-secretase, such as the Notch signalling process.

In one embodiment of the invention, the compound of Formula I is administered to a patient suffering from AD, cerebral amyloid angiopathy, HCHWA-D, multi-infarct dementia, dementia pugilistica or Down syndrome, preferably AD.

In an alternative embodiment of the invention, the compound of Formula I is administered to a patient suffering from mild cognitive impairment or age-related cognitive decline. A favourable outcome of such treatment is prevention or delay of the onset of AD. Age-related cognitive decline and mild cognitive impairment (MCI) are conditions in which a memory deficit is present, but other diagnostic criteria for dementia are absent (Santacruz and Swagerty, *American Family Physician*, **63** (2001), 703-13). (See also "The ICD-10 Classification of Mental and Behavioural Disorders", Geneva: World Health Organisation, 1992, 64-5). As used herein, "age-related cognitive decline" implies a decline of at least six months' duration in at least one of: memory and learning; attention and concentration; thinking; language; and visuospatial functioning and a score of more than one standard deviation below the norm on standardized neuropsychologic testing such as the MMSE. In particular, there may be a progressive decline in memory. In the more severe condition MCI, the degree of memory impairment is outside the range considered normal for the age of the patient but AD is not present. The differential diagnosis of MCI and mild AD is described by Petersen *et al.*, *Arch. Neurol.*, **56** (1999), 303-8. Further information on the differential diagnosis of MCI is provided by Knopman et al, *Mayo Clinic Proceedings*, **78** (2003), 1290-1308. In a study of elderly subjects, Tuokko et al (*Arch, Neurol.*, **60** (2003) 577-82) found that those exhibiting MCI at the outset had a three-fold increased risk of developing dementia within 5 years.

Grundman et al (*J. Mol. Neurosci.*, **19** (2002), 23-28) report that lower baseline hippocampal volume in MCI patients is a prognostic indicator for subsequent AD.

Similarly, Andreasen et al (*Acta Neurol. Scand*, **107** (2003) 47-51) report that high CSF levels of total tau, high CSF levels of phospho-tau and lowered CSF levels of Aβ42 are all associated with increased risk of progression from MCI to AD.

Within this embodiment, the compound of Formula I is advantageously administered to patients who suffer impaired memory function but do not exhibit symptoms of dementia. Such impairment of memory function typically is not attributable to systemic or cerebral disease, such as stroke or metabolic disorders caused by pituitary dysfunction. Such patients may be in particular people aged 55 or over, especially people aged 60 or over, and preferably people aged 65 or over. Such patients may have normal patterns and levels of growth hormone secretion for their age. However, such patients may possess one or more additional risk factors for developing Alzheimer's disease. Such factors include a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; and adult-onset diabetes mellitus.

In a particular embodiment of the invention, the compound of Formula I is administered to a patient suffering from age-related cognitive decline or MCI who additionally possesses one or more risk factors for developing AD selected from: a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; adult-onset diabetes mellitus; elevated baseline hippocampal volume; elevated CSF levels of total tau; elevated CSF levels of phospho-tau; and lowered CSF levels of Aβ(1-42).

A genetic predisposition (especially towards early onset AD) can arise from point mutations in one or more of a number of genes, including the APP, presenilin-1 and presenilin-2 genes. Also, subjects who are homozygous for the ε4 isoform of the apolipoprotein E gene are at greater risk of developing AD.

The patient's degree of cognitive decline or impairment is advantageously assessed at regular intervals before, during and/or after a course of treatment in accordance with the invention, so that changes therein may be detected, e.g. the slowing or halting of cognitive decline. A variety of neuropsychological tests are known in the art for this purpose, such as the Mini-Mental State Examination (MMSE) with norms adjusted for age and education (Folstein *et al.*, *J. Psych. Res.*, **12** (1975), 196-198, Anthony *et al.*, *Psychological Med.*, **12** (1982), 397-408;

Cockrell *et al.*, *Psychopharmacology*, **24** (1988), 689-692; Crum *et al.*, *J. Am. Med. Assoc'n.* 18 (1993), 2386-2391). The MMSE is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive decline or impairment, to estimate the severity of cognitive decline or impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. Another suitable test is the Alzheimer Disease Assessment Scale (ADAS), in particular the cognitive element thereof (ADAS-cog) (See Rosen *et al.*, *Am. J. Psychiatry*, **141** (1984), 1356-64).

Where a variable occurs more than once in formula I or in a substituent thereof, the individual occurrences of that variable are independent of each other, unless otherwise specified.

As used herein, the expression "hydrocarbon group" refers to groups consisting solely of carbon and hydrogen atoms. Such groups may comprise linear, branched or cyclic structures, singly or in any combination consistent with the indicated maximum number of carbon atoms, and may be saturated or unsaturated, including aromatic when the indicated maximum number of carbon atoms so permits unless otherwise indicated.

As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C_{2-6}alkenyl", "hydroxyC_{1-6}alkyl", "heteroarylC_{1-6}alkyl", "C_{2-6}alkynyl" and "C_{1-6}alkoxy" are to be construed in an analogous manner. Most suitably, the number of carbon atoms in such groups is not more than 6.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

The term "heteroaryl" as used herein means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and wherein at least one atom of the aromatic ring is other than carbon. Preferably not more than 3 ring atoms are other than carbon. Examples of heteroaryl groups include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl,

oxadiazolyl, triazolyl and thiadiazolyl groups and benzo-fused analogues thereof. Further examples of suitable heteroaryl ring systems include 1,2,4-triazine, 1,3,5-triazine, 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline. Monocyclic 5- or 6-membered systems are preferred, especially pyridine or thiophene.

For use in medicine, the compounds of formula I may be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, benzenesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Alternatively, where the compound of the invention carries an acidic moiety, a pharmaceutically acceptable salt may be formed by neutralisation of said acidic moiety with a suitable base. Examples of pharmaceutically acceptable salts thus formed include alkali metal salts such as sodium or potassium salts; ammonium salts; alkaline earth metal salts such as calcium or magnesium salts; and salts formed with suitable organic bases, such as amine salts (including pyridinium salts) and quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In formula I, V represents a bond, CH_2 or CH_2CH_2. In a particular embodiment V represents CH_2 and the compounds of formula I are 9-substituted-1,2,3,4-tetrahydrocarbazol-1-yl acetic acid derivatives.

X represents SO_2 or CHR^3 where R^3 represents H or a hydrocarbon group of up to 10 carbon atoms which is optionally substituted as defined previously. X preferably represents CHR^3. Suitable identities for R^3 include H; alkyl (especially C_{1-6}alkyl such as methyl, ethyl, n-propyl, isopropyl, 2-methylpropyl, n-butyl, 3-

methylbutyl and 4-methylpentyl); substituted alkyl (such as methoxymethyl, methylthiomethyl and 3,3,3-trifluoropropyl); alkenyl (such as allyl); cycloalkyl (especially C_{3-6}cycloalkyl such as cyclopropyl, cyclopentyl and cyclohexyl); cycloalkylalkyl (such as cyclopropylmethyl and cyclohexylethyl); aryl (such as phenyl and 4-trifluoromethylphenyl) and arylalkyl (such as benzyl). In a particular embodiment, X represents CHR^3 and R^3 is an optionally-substituted hydrocarbon group of 2 to 10 carbon atoms, preferably 2 to 6 carbon atoms, and in particular an alkyl group of 2 to 6 carbon atoms. Preferred identities for X include CH_2, $CHCH_3$, $CHCH_2CH_3$ and $CHCH_2CH_2CH_3$.

Y represents CO_2H or tetrazole (in particular 1,2,3,4-tetrazol-5-yl), but preferably represents CO_2H.

Ar represents phenyl which is optionally substituted as defined previously. Phenyl groups represented by Ar optionally bear up to 3 substituents as defined previously. When said substituents comprise a group represented by $(CH_2)_m$-Z, m is preferably 0 or 1, most preferably 0. When Ar represents mono-substituted phenyl, the substituent aptly occupies the 4-position. Examples of suitable substituents include halogen (especially Cl and F), N_3, CF_3, OCF_3, OH, OMe, SMe, NHCOMe, SO_2Me, CO_2H, CO_2Me, C_{1-4}alkyl (such as methyl, ethyl, n-propyl and isopropyl), $CON(Me)_2$, COMe, $SO_2N(Me)_2$, $NHSO_2Me$ and NHCONHMe. Preferred substituents include Cl, F, N_3, OCF_3, CF_3 and OMe.

Specific examples of groups represented by Ar include phenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-azidophenyl, 4-methoxyphenyl, 4-trifluoromethoxypheny, 2,4-bis(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 2,4,6-trifluorophenyl and 4-iodophenyl, of which 4-chlorophenyl and 4-trifluoromethylphenyl are particularly preferred.

In Formula I, n is 0, 1, 2, or 3, but is preferably 0, 1 or 2, most preferably 1 or 2. Each R^1 group is independently selected from non-aromatic hydrocarbon of up to 6 carbon atoms and $(CH_2)_q$-W where q is 0, 1 or 2 and W is as defined previously. Preferably, q is 0 or 1, and most preferably q is 0. Non-aromatic hydrocarbon groups represented by R^1 are very aptly linear or branched C_{1-6}alkyl groups such as methyl, ethyl, n-propyl, isopropyl and t-butyl, of which methyl, isopropyl, n-butyl and t-butyl are particularly preferred, or C_{3-6}cycloalkyl, such as cyclopropyl and cyclohexyl.

Examples of groups represented by W include halogen (especially F, Cl and Br), CN, CF_3, OMe, SMe, S(O)Me, SO_2Me, $N(R^4)_2$ (in particular where the R^4 groups complete a heterocyclic ring such as pyrrolidine, piperidine or morpholine) and optionally-substituted phenyl or heteroaryl. Preferred examples of heteroaryl groups represented by W include pyridyl (especially 3-pyridyl) and thiophene (e.g. 3-thienyl). Preferred examples of substituted phenyl groups represented by W include 4-fluorophenyl, 3,4-dichlorophenyl, 3-methylthiophenyl, 2,5-dimethylphenyl and 3-trifluoromethoxyphenyl. Preferred identities for R^1 include methyl, ethyl, isopropyl, n-butyl, t-butyl, cyclopropyl, Br, Cl, F, CN, CF_3, OCH_3, OCF_3, SCH_3, morpholin-1-yl, 4-fluorophenyl, 3,4-dichlorophenyl, 3-methylthiophenyl, 2,5-dimethylphenyl and 3-trifluoromethoxyphenyl.

Each R^2 is independently H or C_{1-4}alkyl such as methyl, ethyl or propyl. Preferably one R^2 is H and the other is H or alkyl. Most preferably, both R^2 groups are H. Alternatively, when p is not zero, one R^2 group together with an R^6 group attached at the same ring position as the $-C(R^2)_2$-Y moiety completes a spiro-linked hydrocarbon ring of 3-6 members, e.g. cyclopropyl.

When present, R^6 represents linear or branched C_{1-6}alkyl (preferably C_{1-4}alkyl) such as methyl, ethyl, n-propyl, isopropyl or t-butyl, C_{2-6} alkenyl such as vinyl or allyl, or phenyl, heteroaryl or benzyl which is optionally substituted as defined previously. Preferred substituents include halogen (especially Cl or F), OCH_3, OCF_3, CF_3 and C_{1-4}alkyl (such as methyl). A preferred heteroaryl group is pyridyl, especially 3-pyridyl. Examples of groups represented by R^6 include methyl, isopropyl, vinyl, 3-pyridyl, phenyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-fluoro-3-methylphenyl, 4-methoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl and 2,5-dimethylphenyl. An R^6 group may be attached at any available position of the ring, including the carbon atom bearing the $-C(R^2)_2$-Y moiety and any carbon atom included in V. Where two R^6 groups are present, they may be the same or different and may be attached to the same or different ring positions. When p is 2, preferably not more than one of the R^6 groups is optionally-substituted phenyl, heteroaryl or benzyl. Alternatively, an R^6 group may combine with an R^2 to complete a spiro-linked ring as defined previously.

Specific examples of compounds suitable for use in the invention include 9-substituted-1,2,3,4-tetrahydrocarbazol-1-yl acetic acid derivatives of formula I in

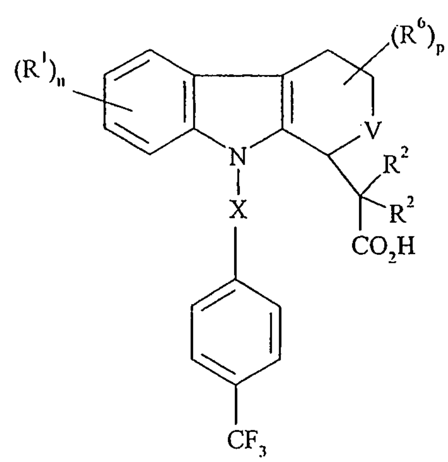
which V is CH_2 and Y is CO_2H and the remaining variables are as indicated in the following table.

Table 1

Compound	$(R^1)_n$	R^2,R^2	$(R^6)_p$	X	Ar
1	6-OMe	H,H	p=0	CH_2	4-Cl-Ph
2	6-F	H,H	p=0	CH_2	4-Cl-Ph
3	6-F	H,H	p=0	CH_2	Ph
4	6-F	H,H	p=0	CH_2	4-MeO-Ph
5	6-F	H,H	p=0	CH_2	3,4-di-Cl-Ph
6	6-Me	H,H	p=0	CH(Me)	4-CF_3-Ph
7	6-F	H,H	p=0	CH(Me)	Ph
8	H	H,H	p=0	CH_2	4-Cl-Ph
9	6-Cl	H,H	p=0	CH_2	4-Cl-Ph
10	5,7-di-Cl	H,H	p=0	CH_2	4-Cl-Ph
11	6-F	H,Me	p=0	CH_2	4-Cl-Ph
12	6-F	H,H	3-Me	CH_2	4-Cl-Ph
13	6-SMe	H,H	p=0	CH_2	4-Cl-Ph
14	6-isopropyl	H,H	p=0	CH_2	4-CF_3-Ph
15	6-isopropyl	H,H	p=0	CH(Me)	4-CF_3-Ph
16	6-isopropyl	H,H	p=0	CH_2	4-Cl-Ph
17	6-isopropyl	H,H	p=0	SO_2	4-CF_3-Ph
18	6-Me, 8-F	H,H	p=0	CH_2	4-CF_3-Ph
19	6-Me, 8-F	H,H	p=0	CH(Me)	4-CF_3-Ph
20	6-isopropyl	H,H	p=0	CH_2	2,4-di-Cl-Ph
21	6-isopropyl	H,H	p=0	CH_2	4-I-Ph
22	6-isopropyl	H,H	p=0	CH_2	2,4,6-tri-F-Ph
23	6,8-di-Cl	H,H	p=0	CH_2	4-CF_3-Ph
24	6,8-di-Me	H,H	p=0	CH_2	4-CF_3-Ph
25	6,8-di-Br	H,H	p=0	CH_2	4-CF_3-Ph
26	6,8-di-Br	H,H	p=0	CH(Me)	4-CF_3-Ph

Compound	$(R^1)_n$	R^2,R^2	$(R^6)_p$	X	Ar
27	8-Cl	H,H	p=0	CH_2	4-CF_3-Ph
28	6-isopropyl	H,H	p=0	CH_2	4-F-Ph
29	6-isopropyl	H,H	p=0	CH_2	4-N_3-Ph
30	6-isopropyl	H,H	3-Ph	CH_2	4-CF_3-Ph
31	6-isopropyl	H,H	p=0	CH(Me)	2,4,6-tri-F-Ph
32	6-isopropyl	H,H	4-(4-F-Ph)	CH_2	4-CF_3-Ph
33	6-isopropyl	H,H	p=0	CH(Et)	4-CF_3-Ph
34	6-isopropyl-8-Br	H,H	p=0	CH_2	4-CF_3-Ph
35	6-isopropyl	H,H	1-Me	CH_2	4-CF_3-Ph
36	5-(4-F-Ph)	H,H	p=0	CH_2	4-CF_3-Ph
37	6-isopropyl	H,H	1-Me, 4-vinyl	CH_2	4-CF_3-Ph

A subset of the compounds of Formula I is defined by Formula II:



II

wherein V, X, n, p, R^1, R^2 and R^6 have the same definitions and preferred identities as before.

With the exception of the compound in which V is CH_2, X is CH_2, p is 0, each R^2 is H, and $(R^1)_n$ represents 6,8-difluoro, the compounds of Formula II in which V is CH_2 or CH_2CH_2 and the pharmaceutically acceptable salts thereof are believed to be novel, and hence constitute a further aspect of the invention. The invention further extends to pharmaceutical compositions comprising, in a pharmaceutically acceptable carrier, a compound of Formula II wherein V is CH_2 or CH_2CH_2 or a pharmaceutically acceptable salt thereof, with the exception of the compound in which V is CH_2, X is CH_2, p is 0, each R^2 is H, and $(R^1)_n$ represents 6,8-difluoro.

In Formula II, X is preferably CHR^3, in particular CH_2, CH(Me), CH(Et) or CH(Pr). Particularly preferred examples include the compounds:

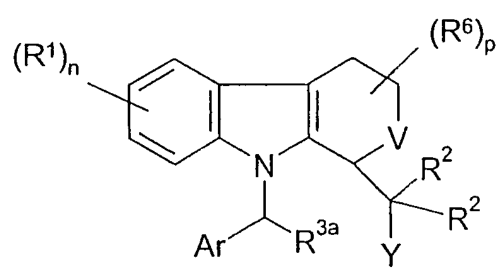
{6-isopropyl-9-[1-(4-trifluoromethylphenyl)ethyl]-2,3,4,9-tetrahydro-1H-carbazol-1-yl}-acetic acid; and

{6-isopropyl-9-[1-(4-trifluoromethylphenyl)propyl]-2,3,4,9-tetrahydro-1H-carbazol-1-yl}-acetic acid; and

{6-isopropyl-9-[1-(4-trifluoromethylphenyl)butyl]-2,3,4,9-tetrahydro-1H-carbazol-1-yl}-acetic acid.

Compounds of Formula I in which p is 1 or 2 and at least one R^6 represents C_{2-6}alkenyl or phenyl, heteroaryl or benzyl which are optionally substituted as described previously are also novel, and said compounds, their pharmaceutically acceptable salts, and pharmaceutical compositions comprising them constitute a further aspect of the invention. In this context, V is preferably CH_2, p is preferably 1 and R^6 is preferably optionally substituted phenyl, such as phenyl or 4-fluorophenyl, attached to the 3-position or the 4-position of the tetrahydrocarbazole ring.

A further novel subset of the compounds of formula I is defined by formula III:



III

wherein R^{3a} represents a hydrocarbon group containing from 2 to 10 carbon atoms which is optionally substituted with halogen, CF_3, C_{1-4}alkoxy or C_{1-4}alkylthio;

and V, Y, Ar, n, p, R^1, R^2 and R^6 have the same definitions and preferred identities as before, with the proviso that R^1 does not represent SOR^4 or SO_2R^4.

Compounds of formula III and pharmaceutically acceptable salts thereof constitute a further aspect of the invention. The invention further extends to pharmaceutical compositions comprising a compound of formula III or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In the compounds of formula III, R^{3a} very aptly represents C_{3-6}alkyl, in particular n-propyl. V is very aptly CH_2. Ar is very aptly 4-trifluoromethylphenyl. Y is preferably CO_2H. Preferably at least one R^2 is H and most preferably both R^2 groups represent H.

Specific examples of compounds in accordance with formula III include 9-substituted-1,2,3,4-tetrahydrocarbazol-1-yl acetic acid derivatives in which V represents CH_2, Y represents CO_2H, Ar represents 4-trifluoromethylphenyl, each R^2 is H (unless otherwise indicated) and the other variables are as shown in table 2:

Table 2

Cpd.	$(R^1)_n$	$(R^6)_p$	R^{3a}
33	6-isopropyl	p=0	ethyl
38	6-isopropyl	p=0	propyl
39	6,8-dichloro	p=0	ethyl
40	6-isopropyl	4,4-di-Me	ethyl
41	5-bromo	p=0	n-propyl
42	5-(3,4-di-Cl-Ph)	p=0	ethyl
43	6,8-dichloro	p=0	n-propyl
44	5,7-dichloro	p=0	n-propyl
45	6-chloro	p=0	n-propyl
46	6-isopropyl	p=0	2-methylpropyl
47	8-chloro	p=0	n-propyl
48	n=0	p=0	n-propyl
49	6-isopropyl	4-(4-F-Ph)	n-propyl
50	6-isopropyl	p=0	$4\text{-}CF_3\text{-Ph}$

Cpd.	$(R^1)_n$	$(R^6)_p$	R^{3a}
51	6-bromo	p=0	n-propyl
52	6-(3,4-di-Cl-Ph)	p=0	n-propyl
53	6,8-difluoro	p=0	n-propyl
54	6-isopropyl	p=0	cyclohexyl
55	6-isopropyl	p=0	isopropyl
56	6-isopropyl	p=0	methoxymethyl
57	5-(3,4-di-Cl-Ph)	p=0	n-propyl
58	6-n-butyl	p=0	n-propyl
59	8-Cl-6-isopropyl	p=0	n-propyl
60	5-(3-OCF_3-Ph)	p=0	n-propyl
61	5-OCF_3	p=0	n-propyl
62	6-isopropyl	p=0	n-butyl
63	5-CN	p=0	n-propyl
64	6-isopropyl	p=0	3-methylbutyl
65	5-(morpholin-1-yl)	p=0	n-propyl
66	6-isopropyl	p=0	3,3,3-trifluoropropyl
67	6-cyclopropyl	p=0	n-propyl
68	7-cyclopropyl	p=0	n-propyl
69	7-bromo	p=0	n-propyl
70	5-cyclopropyl	p=0	n-propyl
71	6-CN	p=0	n-propyl
72	5-isopropyl	p=0	n-propyl
73	5-(3,4-di-Cl-Ph)-6-isopropyl	p=0	n-propyl
74	6-isopropyl	p=0	methylthiomethyl
75	6-t-butyl	p=0	n-propyl
76	6-isopropyl	p=0	allyl
77	6-isopropyl	p=0	cyclohexylethyl
78	6-isopropyl	p=0	4-methylpentyl
79	6-isopropyl	1-^{n}propyl	n-propyl

Cpd.	$(R^1)_n$	$(R^6)_p$	R^{3a}
80	6-isopropyl	*1-spiro-cyclopropyl	n-propyl

* together with R^2

Further examples of specific compounds in accordance with formula III include those of the following formula wherein the variables are as shown in table 3:

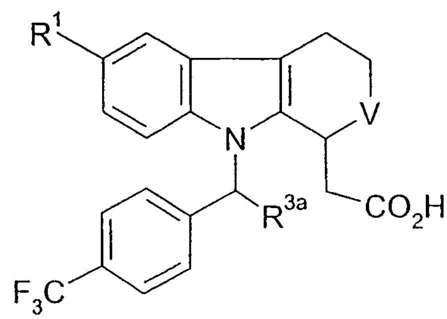
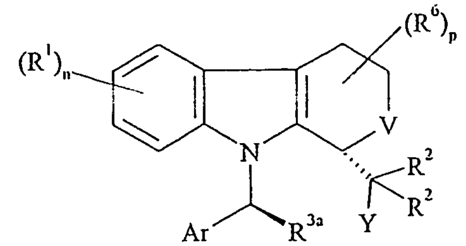


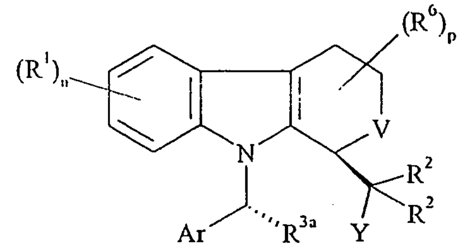
Table 3

Compound	V	R^1	R^{3a}
81	bond	isopropyl	n-propyl
82	CH_2CH_2	isopropyl	n-propyl

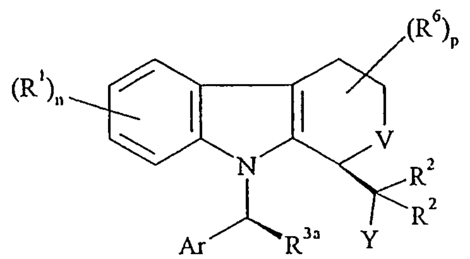
It will be apparent to those skilled in the art that in formula III the carbon atom to which R^{3a} is attached and the carbon atom to which $C(R^2)_2$-Y is attached are both chiral centres, and hence that the relevant compounds exist in at least two diastereomeric and at least four enantiomeric forms:



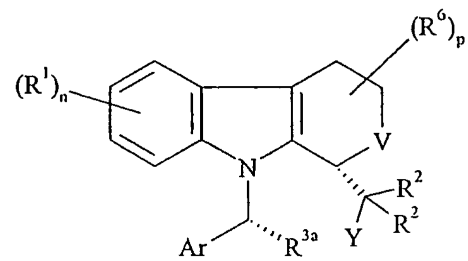
(IIIA)



(IIIB)



(IIIC)

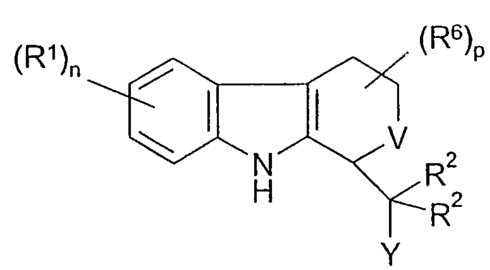


(IIID)

where V, Y, Ar, n, p, R^1, R^2, R^{3a} and R^6 have the same meanings as before.

It is to be understood that all such isomers are included within the scope of the invention, as pure compounds or as mixtures of isomers in any proportion.

Compounds of Formula I in which X is SO_2 may be prepared by reaction of compounds (1) with $ArSO_2Cl$:



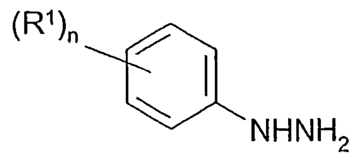
(1)

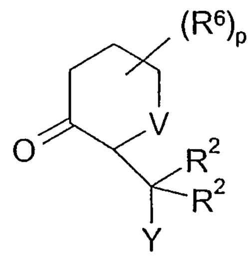
where V, Ar, Y, n, p, R^1, R^2 and R^6 have the same meanings as before. The reaction takes place in the presence of a base such as triethylamine in an aprotic solvent.

Compounds of formula I in which X is CHR^3 may be prepared by N-alkylation of compounds of formula (1) with $ArCH(R^3)$-L where L is a leaving group such as Cl, Br, I, mesylate, tosylate or triflate, and Ar and R^3 have the same meaning as before. The N-alkylation may be carried out by treating the compound of formula I with

strong base such as sodium hydride or potassium t-butoxide in DMF at about 0°C, then adding $ArCH(R^3)$-L and warming to ambient temperature.

Compounds of formula (1) may be prepared by the well-known Fischer indole synthesis route, involving condensation of a hydrazine (2) with a ketone (3):

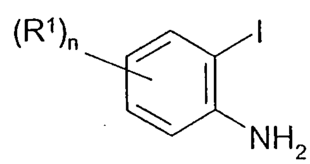




(2) (3)

where V, Y, n, p, R^1, R^2 and R^6 have the same meanings as before. The reaction may be carried out by refluxing in a lower alkanol.

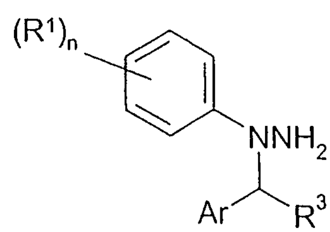
An alternative route to compounds of formula (1) involves reaction of a ketone (3) with an iodoaniline (4):



(4)

where n and R^1 have the same meaning as before. The reaction takes place in DMF solution in the presence of $Si(OEt)_4$ and an acid such as toluenesulphonic acid, followed by treatment with palladium acetate and Hunig's base.

Compounds of formula I in which X is CHR^3 may also be prepared directly by the Fischer indole route using a hydrazine of formula (5) instead of the hydrazine of formula (2):

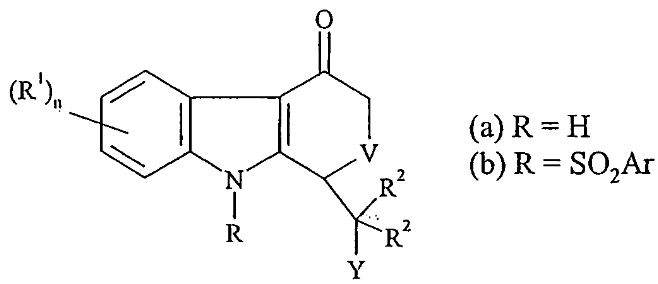


(5)

where Ar, n, R^1 and R^3 have the same meaning as before. EP0234708 discloses detailed procedures for the Fischer indole route applied to ketones (3) in which V is

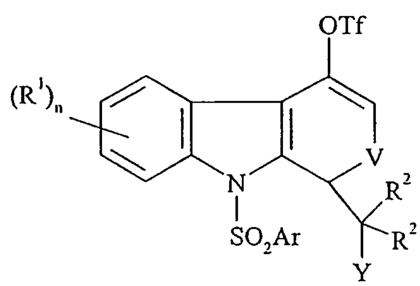
CH_2. These procedures are equally applicable to ketones (3) in which V is a bond or CH_2CH_2.

A preferred route compounds of formula I in which p is 1 and R^6 is attached as shown in compounds (9) below comprises oxidation of compounds (1) in which p is 0 to form ketones (6a), followed by treatment with $ArSO_2Cl$ to give sulfonamides (6b):



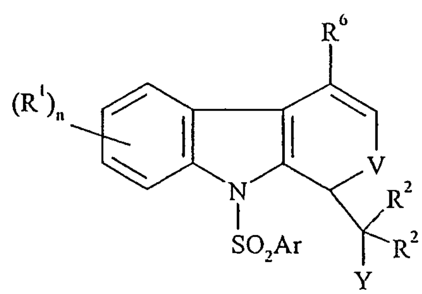
(6)

followed by conversion to the corresponding enol triflates (7):



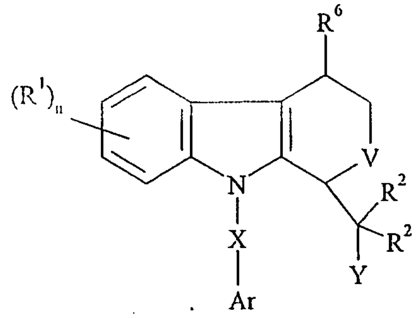
(7)

followed by treatment with R^6-$B(OH)_2$ to give the compounds of formula (8):



(8)

followed by hydrogenation to give the compounds of formula (9a):



(a) $X = SO_2$
(b) $X = CHR^3$

(9)

where Tf represents trifluoromethanesulfonyl (triflyl) and n, R^1, R^2, R^6, V, Y and Ar have the same meanings as before.

In the above scheme, R^6 very suitably represents phenyl or substituted phenyl, such as 4-fluorophenyl.

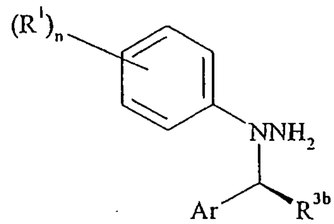
The oxidation to form ketones (6a) may be carried out using DDQ in aqueous THF at about 0°C, while the treatment with $ArSO_2Cl$ may be carried out as described previously. Formation of triflates (7) takes place in THF at low temperature (e.g. –78°C) in the presence of strong base (such as lithium hexamethyldisilazide) and N-phenylbis(trifluoromethanesulfonimide). Treatment with R^6-$B(OH)_2$ may be carried out in dioxan at about 80°C in the presence of potassium phosphate and $Pd(PPh_3)_4$. The hydrogenation may be carried out over a Pd/C catalyst in ethyl acetate.

The corresponding compounds (9b) (in which X represents CHR^3) may be prepared by treatment of compounds (8) in which Ar is 4-methylphenyl with sodium amalgam and NaH_2PO_4, followed by N-alkylation of the detosylated product with $ArCH(R^3)$-L, then hydrogenation as before, where L is a leaving group such as Cl, Br, I, mesylate, tosylate or triflate, and R^3 has the same meaning as before. The treatment with sodium amalgam and NaH_2PO_4 may be carried out at ambient temperature in a THF – methanol mixture. The N-alkylation may be carried out by treating the detosylated product with sodium hydride in DMF at about 0°C, then adding $ArCH(R^3)$-L and warming to ambient temperature.

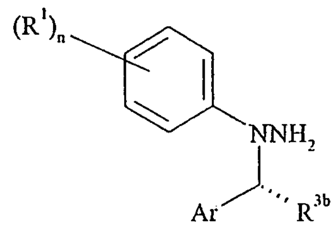
During all of the chemical processes described above, a carboxylic acid group represented by Y is preferably protected as the methyl ester or ethyl ester, the free acid being regenerated by hydrolysis in a final step, e.g. using LiOH in aqueous THF.

Since the compounds of Formula I have at least one asymmetric centre, they accordingly exist in enantiomeric forms. If desired, the individual enantiomers may be isolated in pure form by conventional means. For example, a racemic mixture may be resolved into its component enantiomers by preparative chiral HPLC, or by treatment with an optically pure amine to form diastereomeric salt pairs, separable by fractional crystallisation, from which the optically pure acids may be regenerated. Similarly, a racemic acid may be reacted with an optically pure alcohol or amine to form pairs of diastereomeric esters or amides which may be separated by chromatography or fractional crystallisation and hydrolysed to yield enantiomerically-pure acids. These resolution techniques may equally well be practised on the synthetic precursors of the compounds of Formula I, and the resulting optically-pure intermediates used to prepare compounds of Formula I in optically-pure form.

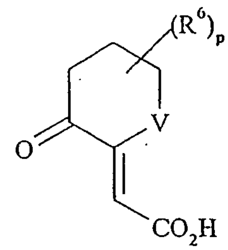
A preferred synthetic route, capable of providing single enantiomers such as those of formula IIIA, IIIB, IIIC or IIID in which Y is CO_2H and both R^2 groups are H involves condensation of a hydrazine (5a) or 5(b) with an acrylic acid derivative (10) to form (11a) or (11b) respectively, followed by asymmetric hydrogenation of the exocyclic double bond:



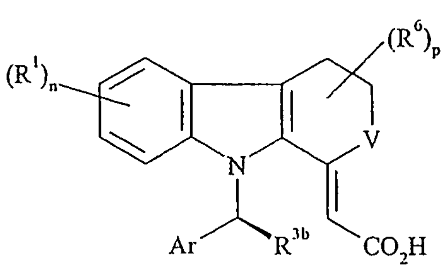
(5a)



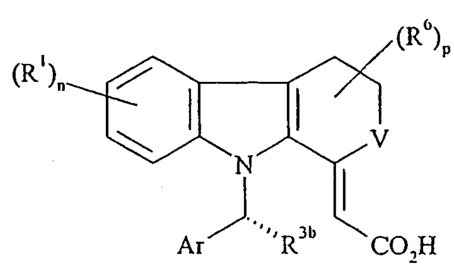
(5a)



(10)



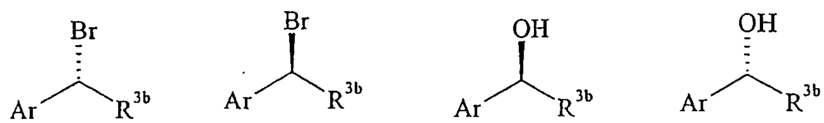
(11a)



(11b)

where V, Ar, n, p, R^1 and R^6 have the same meanings as before, and R^{3b} is R^3 that is other than H. The condensation is preferably carried out using excess of (10) in refluxing isopropanol in the presence of toluenesulphonic acid and molecular sieves. The hydrogenation is preferably carried out in a lower alkanol such as methanol over a chiral Ru(BINAP)Cl_2 catalyst, where BINAP is bis(diphenylphosphino)-1,1'-binaphthyl. Hydrogenation of (11a) over Ru(S-BINAP)Cl_2 is preferred.

Chiral hydrazines (5a) and (5b) may be obtained by alkylation of hydrazines (2) with chiral bromides (12a) and (12b) respectively, which in turn are obtainable, respectively, by treatment of chiral alcohols (13a) and (13b) with carbon tetrabromide and triphenylphosphine:



(12a) (12b) (13a) (13b)

The alkylation may be carried out in THF in the presence of strong base such as sodium hexamethyldisilazide. The bromination is typically carried out in dichloromethane solution.

Chiral alcohols (13a) and (13b) are obtainable by asymmetric reduction of ketones Ar-CO-R^{3b}, where Ar and R^{3b} have the same meanings as before. Any suitable chiral reducing agent may be used, but in a preferred method reduction is effected using borane in the presence of a chiral oxazaborolidine (OAB) catalyst (see Corey, *Angew, Chem. Int. Ed. Engl.*, 37 (1998), 1986). The reaction may be carried out in a dichloromethane/toluene mixture at -30°C. Use of (R)-OAB provides alcohol (13a) and (ultimately) hydrazine (5a). Use of (S)-OAB provides alcohol (13b) and (ultimately) hydrazine (5b).

The compounds of Formula I are typically used in the form of pharmaceutical compositions comprising one or more compounds of Formula I and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. The principal

active ingredient typically is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate, or gums, dispersing agents, suspending agents or surfactants such as sorbitan monooleate and polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a homogeneous preformulation composition containing a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. Tablets or pills of the composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compositions useful in the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) or gelatin.

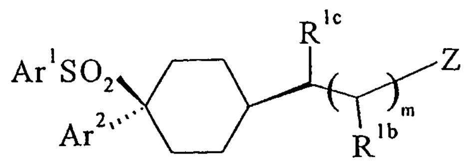
For treating or preventing Alzheimer's disease, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, and more preferably about 0.05 to 50 mg/kg of body weight per day, of the active compound. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, a dosage outside these limits may be used.

The compounds of Formula I optionally may be administered in combination with one or more additional compounds known to be useful in the treatment or prevention of AD or the symptoms thereof. Such additional compounds thus include cognition-enhancing drugs such as acetylcholinesterase inhibitors (e.g. donepezil and galanthamine), NMDA antagonists (e.g. memantine) or PDE4 inhibitors (e.g. Ariflo™ and the classes of compounds disclosed in WO 03/018579, WO 01/46151, WO 02/074726 and WO 02/098878). Such additional compounds also include cholesterol-lowering drugs such as the statins, e.g. simvastatin. Such additional compounds similarly include compounds known to modify the production or processing of Aβ in the brain ("amyloid modifiers"), such as compounds which inhibit the secretion of Aβ (including γ-secretase inhibitors, β-secretase inhibitors, and GSK-3α inhibitors), compounds which inhibit the aggregation of Aβ, and antibodies which selectively bind to Aβ.

In this embodiment of the invention, the amyloid modifier may be a compound which inhibits the secretion of Aβ, for example an inhibitor of of γ-secretase (such as those disclosed in WO 01/53255, WO 01/66564, WO 01/70677, WO 01/90084, WO 01/77144, WO 02/30912, WO 02/36555, WO 02/081435, WO 02/081433, WO 03/018543, WO 03/013506, WO 03/013527, WO 03/014075, WO 03/093252, WO 03/093264, WO 03/093251, WO 03/093253, WO 2004/039800 and WO 2004/039370), or a β-secretase inhibitor (such as those disclosed in WO 03/037325, WO 03/030886, WO 03/006013, WO 03/006021, WO 03/006423, WO 03/006453, WO 02/002122, WO 01/70672, WO 02/02505, WO 02/02506, WO 02/02512, WO 02/02520, WO 02/098849 and WO 02/100820), or any other compound which inhibits the formation or release of Aβ including those disclosed in WO 98/28268, WO 02/47671, WO 99/67221, WO 01/34639, WO 01/34571, WO 00/07995, WO 00/38618, WO 01/92235, WO 01/77086, WO

01/74784, WO 01/74796, WO 01/74783, WO 01/60826, WO 01/19797, WO 01/27108, WO 01/27091, WO 00/50391, WO 02/057252, US 2002/0025955 and US2002/0022621, and also including GSK-3 inhibitors, particularly GSK-3α inhibitors, such as lithium, as disclosed in Phiel et al, *Nature*, **423** (2003), 435-9.

Within this embodiment, the amyloid modifier is advantageously a γ-secretase inhibitor, preferred examples of which include a compound of formula XI:

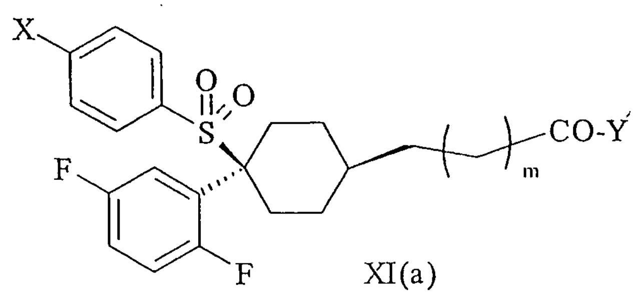


XI

wherein m, R^{1b}, R^{1c}, Z, Ar^1 and Ar^2 are as defined in WO 03/018543;

or a pharmaceutically acceptable salt thereof.

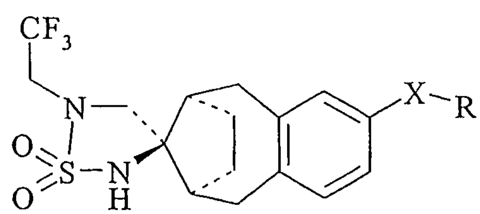
Such compounds may be prepared as described in WO 03/018543. Preferred examples include those defined by formula XIa:



XI(a)

and the pharmaceutically acceptable salts thereof, wherein m is 0 or 1, X is Cl or CF_3, and Y is OH, OC_{1-6}alkyl, NH_2 or NHC_{1-6}alkyl. Particular examples include those in which m is 1 and Y is OH (or the sodium salts thereof), and those in which m is 0 and Y is NH_2 or NHC_{1-6}alkyl.

Another preferred class of γ-secretase inhibitors for use in this embodiment of the invention is that defined by formula XII:



XII

wherein X and R are as defined in WO 03/093252;
or a pharmaceutically acceptable salt thereof.

X is very aptly 5-substituted-thiazol-2-yl, 5-substituted-4-methylthiazol-2-yl, 5-substituted-1-methylpyrazol-3-yl, 1-substituted-imidazol-4-yl or 1-substituted-1,2,4-triazol-3-yl. Preferably, R represents optionally-substituted phenyl or heteroaryl such as phenyl, monohalophenyl, dihalophenyl, trihalophenyl, cyanophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, trifluoromethoxyphenyl, pyridyl, monohalopyridyl and trifluoromethylpyridyl, wherein "halo" refers to fluoro or chloro. Particularly preferred identities of R-X- include 5-(4-fluorophenyl)-1-methylpyrazol-3-yl, 5-(4-chlorophenyl)-1-methylpyrazol-3-yl and 1-(4-fluorophenyl)imidazol-4-yl. Such compounds may be prepared by methods disclosed in WO 03/093252.

Alternatively, the amyloid modifier may be a compound which inhibits the aggregation of Aβ. Suitable examples include chelating agents such as clioquinol (Gouras and Beal, *Neuron*, **30** (2001), 641-2) and the compounds disclosed in WO 99/16741, in particular that known as DP-109 (Kalendarev et al, *J. Pharm. Biomed. Anal.*, **24** (2001), 967-75). Other inhibitors of Aβ aggregation suitable for use in the invention include the compounds disclosed in WO 96/28471, WO 98/08868 and WO 00/052048, including the compound known as Apan™ (Praecis); WO 00/064420, WO 03/017994, WO 99/59571 and the compcund known as Alzhemed™ (Neurochem); WO 00/149281 and the compositions known as PTI-777 and PTI-00703 (ProteoTech); WO 96/39834, WO 01/83425, WO 01/55093, WO 00/76988, WO 00/76987, WO 00/76969, WO 00/76489, WO 97/26919, WO 97/16194, and WO 97/16191.

Alternatively, the amyloid modifier may be an antibody which binds selectively to Aβ. Said antibody may be polyclonal or monoclonal, but is preferably monoclonal, and is preferably human or humanized. Preferably, the antibody is capable of sequestering soluble Aβ from biological fluids, as described in WO 03/016466, WO 03/016467, WO 03/015691 and WO 01/62801. Suitable antibodies include humanized antibody 266 (described in WO 01/62801) and the modified version thereof described in WO 03/016466.

As used herein, the expression "in combination with" requires that therapeutically effective amounts of both the compound of Formula I and the additional compound are administered to the subject, but places no restriction on the

manner in which this is achieved. Thus, the two species may be combined in a single dosage form for simultaneous administration to the subject, or may be provided in separate dosage forms for simultaneous or sequential administration to the subject. Sequential administration may be close in time or remote in time, e.g. one species administered in the morning and the other in the evening. The separate species may be administered at the same frequency or at different frequencies, e.g. one species once a day and the other two or more times a day. The separate species may be administered by the same route or by different routes, e.g. one species orally and the other parenterally, although oral administration of both species is preferred, where possible. When the additional compound is an antibody, it will typically be administered parenterally and separately from the compound of Formula I.

In a further aspect, the invention provides the combination of a compound of formula I or a pharmaceutically acceptable salt thereof and a compound of formula XI(a) or a pharmaceutically acceptable salt thereof for use in treatment or prevention of a disease associated with deposition of β-amyloid in the brain. Said use may involve the simultaneous or separate administration of the respective compounds to a patient in need of such treatment or prevention.

In a further aspect, the invention provides a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I or a pharmaceutically acceptable salt thereof and a compound of formula XI(a) or a pharmaceutically acceptable salt thereof. Preferably, the pharmaceutical composition is in a unit dose form suitable for oral administration, such as a tablet or a capsule.

EXAMPLES

The ability of the compounds of Formula I to selectively inhibit production of Aβ(1-42) was determined using the following assay:

Cell-based γ-Secretase Assay

Human SH-SY5Y neuroblastoma cells overexpressing the direct γ-secretase substrate SPA4CT were induced with sodium butyrate (10 mM) for 4 hours prior to

plating. Cells were plated at 35,000 cells/well/100 μl in 96-well plates in phenol red-free MEM/10% FBS, 50 mM HEPES, 1% Glutamine and incubated for 2 hrs at 37 °C, 5% CO_2.

Compounds for testing were diluted into Me_2SO to give a ten point dose-response curve. Typically 10 μl of these diluted compounds in Me_2SO were further diluted into 182 μl dilution buffer (phenol red-free MEM/10% FBS, 50 mM HEPES, 1% Glutamine) and 10 μl of each dilution was added to the cells in 96-well plates (yielding a final Me_2SO concentration of 0.5%). Appropriate vehicle and inhibitor controls were used to determine the window of the assay.

After incubation overnight at 37 °C, 5%CO_2, 10 μl and 50 μl media were transferred into a fresh Costar round-bottom 96-well plate for detection of Aβ(40) and Aβ(42) peptides, respectively. 40 μl Origen buffer (PBS, 2% BSA, 0.2% Tween-20) was added to the Aβ(40) wells followed by the addition of 25 μl the respective antibody premixes to the wells:

Aβ(40) premix: 1 μg/ml ruthenylated G2-10 antibody, 4 μg/ml biotinylated 4G8 antibody diluted in Origen buffer

Aβ(42) premix: 0.5 μg/ml ruthenylated G2-11 antibody, 4 μg/ml biotinylated 4G8 antibody diluted in Origen buffer

(Biotinylated 4G8 antibody supplied by Signet Pathology Ltd; G2-10 and G2-11 antibodies supplied by Chemicon)

After overnight incubation of the assay plates on a shaker at 4 °C, the Origen M8 Analyser (Igen Inc.) was calibrated according to the manufacturer's instructions. 25 μl of streptavidin magnetic bead (Dynal) premix (400 μg/ml streptavidin beads/ml in Origen buffer) was added to the assay plates and incubated on a shaker for 15 minutes. 150 μl Origen buffer was added to each well and the plates were read on the Origen M8 Analyser according to the manufacturer's instructions.

Cell viability was measured in the corresponding cells after removal of the media for the Aβ assays by a colorimetric cell proliferation assay (CellTiter 96™ AQ assay, Promega) utilizing the bioreduction of MTS (Owen's reagent) to formazan

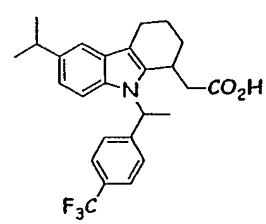
according to the manufacturer's instructions. Briefly, 5 μl of 10x MTS/PES was added to the remaining 50 μl of media before returning to the incubator. The optical density was read at 495 nm after ~4 hours.

LD_{50} and IC_{50} values for inhibition of Aβ(40) and Aβ(42) were calculated by nonlinear regression fit analysis using the appropriate software (eg. Excel fit). The total signal and the background were defined by the corresponding Me_2SO and inhibitor controls.

The compounds listed in Tables 1-3 above all gave IC_{50} values for Aβ(1-42) inhibition that were at least 2-fold lower than the corresponding IC_{50} values for Aβ(1-40) inhibition, typically at least 5-fold lower, and in the preferred cases at least 50-fold lower.

EXAMPLE 1

{6-Isopropyl-9-[1-(4-trifluoromethyl-phenyl)-ethyl]-2,3,4,9-tetrahydro-1H-carbazol-1-yl}-acetic acid



Step 1

To a stirred solution of 4-isopropylphenylhydrazine hydrochloride (8.35g, 45mmol.) in ethanol (300ml) was added ethyl 2-cyclohexanoneacetate (8.23g, 45mmol.) and the mixture heated to reflux for 16 hours. Upon cooling, the solvent was evaporated and the residue taken up in ethyl acetate (200ml) and washed with 1N HCl (200ml). The aqueous was extracted with further ethyl acetate (200ml) and the combined organics washed with brine (100ml), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography eluting with ether: hexane (1:3) to afford the desired tetrahydrocarbazole (5.1g). ^1H NMR ($CDCl_3$) 8.60 (1H, br s), 7.29 (1H, d,

J=1.0Hz), 7.21 (1H, d, J=8.5Hz), 7.01 (1H, dd, J=8.5, 1.0Hz), 4.20 (2H, q, J=7.0Hz), 3.34 (1H, m), 2.99 (1H, septet, J=7.0Hz), 2.71-2.54 (4H, m), 2.05 (1H, m), 1.95-1.75 (2H, m), 1.69-1.57 (1H, m), 1.30 (6H, d, J=7.0Hz), 1.28 (3H, t, J=7.0Hz). m/z =300 $[MH]^+$

Step 2

To a degassed solution of the tetrahydrocarbazole from the foregoing step (448mg, 1.50mmol) in DMF (10ml) was added potassium tert-butoxide (201mg, 1.8mmol.). The resulting red/brown solution was stirred at ambient temperature for 10 minutes before a solution of 1-(1-bromoethyl)-4-trifluoromethylbenzene (417mg, 1.65mmol.) in DMF (2ml) was added. After stirring an additional 2.75 hours, the colour had faded to pale yellow and the reaction was quenched by the addition of 2N HCl (50ml). The mixture was extracted with ethyl acetate (2x100ml) and the combined organics washed with further 2N HCl (100ml), water (100ml) and brine (100ml), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography eluting with ether: hexane (1:6) to afford the desired N-benzylated tetrahydrocarbazole (376mg) as a 3:2 mixture of diastereomers (designated isomer A and isomer B respectively). ^{1}H NMR ($CDCl_3$) 7.56 (2H, d, J=8.5Hz, isomer B), 7.50 (2H, d, J=8.5Hz, isomer A), 7.33 (3H [isomer B] + 1H [isomer A], m), 7.19 (2H, d, J=8.5Hz, isomer A), 6.87-6-81 (2H [isomer A] + 1H [isomer B], m), 6.63 (1H, d, J=8.5Hz, isomer B), 5.63 (1H, br q, J=7.0Hz, isomers A+B), 4.24-4.02 (2H, m, isomers A+B), 3.49 (1H, br d, J=10Hz, isomers A+B), 3.00-2.83 (2H, m, isomers A+B), 2.73-2.37 (4H, m, isomers A+B), 2.05 (3H, d, J=7.0Hz, isomer A), 2.01-1.80 (3H, m, isomers A+B), 1.87 (3H, d, J=7.0Hz, isomer B), 1.32-1.18 (9H, m, isomers A+B). m/z =472 $[MH]^+$.

Step 3

To a solution of the ester from the foregoing step (376mg, 0.80mmol.) in THF (20ml) was added a solution of lithium hydroxide (200mg) in water (10ml) and the mixture stirred vigorously at 60°C for 4 hours. Upon cooling, the mixture was partitioned between ethyl acetate (50ml) and 2N HCl (50ml). The aqueous was extracted with further ethyl acetate (50ml) and the combined organics washed with water (50ml) and

brine (50ml), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography eluting with acetic acid: ethyl acetate: hexane (0:33:100 to 1:33:100) to afford the desired product (340mg) as a 3:2 mixture of diastereomers (designated isomer A and isomer B respectively). ^{1}H NMR ($CDCl_3$) 11.5-9.5 (1H, v br s, isomer A+B), 7.57 (2H, d, J=8.5Hz, isomer B), 7.51 (2H, d, J=8.5Hz, isomer A), 7.33 (3H [isomer B] + 1H [isomer A], m), 7.18 (2H, d, J=8.5Hz, isomer A), 6.86-6-82 (2H [isomer A] + 1H [isomer B], m), 6.64 (1H, d, J=8.5Hz, isomer B), 5.60 (1H, br q, J=7.0Hz, isomers A+B), 3.49 (1H, m, isomers A+B), 3.01-2.81 (2H, m, isomers A+B), 2.75-2.43 (4H, m, isomers A+B), 2.05 (3H, d, J=7.0Hz, isomer A), 2.01-1.80 (3H, m, isomers A+B), 1.88 (3H, d, J=7.0Hz, isomer B), 1.26 (6H, m, isomers A+B). m/z =444 $[MH]^+$.

This racemic mixture of diastereomers could be efficiently separated into the four individual stereoisomers by supercritical fluid chromatography using a Berger Instruments Minigram SFC. Column: Chiralcel OJ-H 250x10mm (5μ) [Chiral Technologies] at oven temperature 35°C, eluent CO_2 + 8% [MeOH+0.1% diethylamine] modifier run at 10ml/min with CO_2 outlet pressure 100 bar; detection at 220nm.

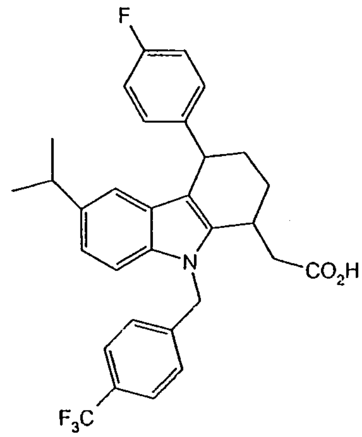
Isomer B, ent. 1 at 5.68 min.; Isomer B, ent. 2 at 6.21 min.; Isomer A, ent. 1 at 7.19 min.; Isomer A, ent. 2 at 9.49 min.

Preparation of 1-(1-bromoethyl)-4-trifluoromethylbenzene.

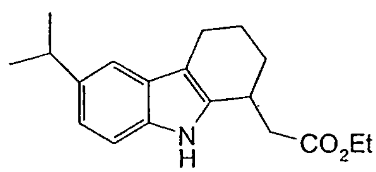
To a stirred solution of 1-(4-trifluoromethylphenyl)-ethanol (4.2g, 22mmol.) in dichloromethane (60ml) under nitrogen was added dropwise phosphorus tribromide (2.3ml, 24mmol.). The reaction was stirred 1 hour at ambient temperature then quenched by the addition of water (20ml). The organic layer was washed with further water (30ml), a saturated solution of sodium bicarbonate (30ml) and brine (30ml) then dried ($MgSO_4$) and evaporated to afford the product (3.6g). ^{1}H NMR ($CDCl_3$) 7.60 (2H, d, J=8.5Hz), 7.54 (2H, d, J=8.5Hz), 5.19 (1H, q, J=7.0Hz), 2.04 (3H, d, J=7.0Hz).

EXAMPLE 2

{4-(4-fluorophenyl)-6-isopropyl-9-[(4-trifluoromethylphenyl)methyl]-1,2,3,4-tetrahydrocarbazole-1-yl} acetic acid

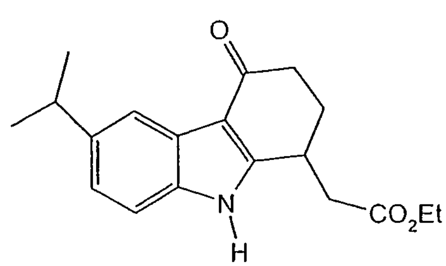


Step 1



Available by the procedure described in EP0234708, Example 34 Step 1, using 4-isopropylphenylhydrazine hydrochloride.

Step 2

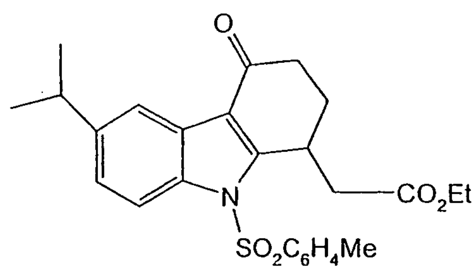


The product of Step 1 (5.0 g, 16.7 mmol) in degassed THF (170 ml) and water (15 ml), under nitrogen, was cooled to 0^0C and DDQ (9.3 g, 41.4 mmol) in degassed THF (60 ml) was added dropwise over 15 min. After 3 h at 0^0C the mixture was concentrated, the residue taken up in ethyl acetate (200 ml), then washed with

saturated aqueous sodium hydrogencarbonate (5x50 ml), water, brine, dried ($MgSO_4$) and evaporated to give a tan solid (4.8 g).

m/z =314 $[MH]^+$

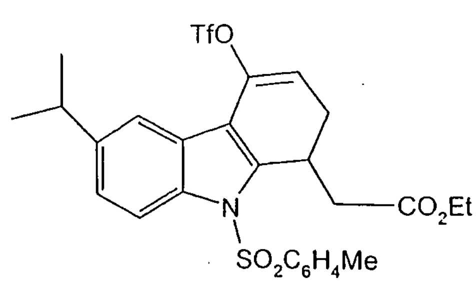
Step 3



The product of Step 2 (1,6 g, 7.5 mmol) in dry DMF (25 ml) was cooled to 0^0C under nitrogen. Sodium hydride (60% dispersion in mineral oil, 450 mg, 11.3 mmol) was added portionwise over 15 min. After stirring at 0^0C for 20 min, tosyl chloride (2.1 g, 11.3 mmol) in dry toluene (25 ml) was added dropwise. The reaction was stirred at 0^0C for 1 h and then allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with saturated aqueous ammonium chloride (5 ml), diluted with water (500 ml) and extracted with ethyl acetate (3x100 ml). The organic extracts were washed with water (2x 50 ml), brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography eluting with 9:1 ^{i}hexane/ethyl acetate to 4:1 ^{i}hexane/ethyl acetate to afford a light brown foam (1.9 g). ^1H NMR ($CDCl_3$) 8.10 (2H, dd, J= 8.4, 1.8Hz), 7.73 (2H, d, J = 8.4 Hz), 7.32 (3H, m), 4.23 (2H, q, J = 7.0Hz), 3.05-2.98 (2H, m), 2.75-2.65 (2H, m), 2.53-2.48 (2H, m), 2.37 (3H, s), 2.30-2.20 (2H, m), 1.30 (6H, d, J=7.1Hz), 1.27 (3H, t, J = 7.0Hz).

m/z = 468 $[MH]^+$

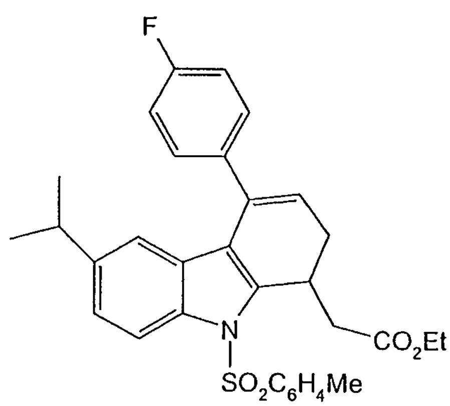
Step 4



To the product of Step 3 (1.7 g, 4.6 mmol) in dry THF (20 ml) under nitrogen and cooled to -78^0C was added lithium hexamethyldisilazide (1 M solution in THF, 7 ml, 7 mmol) dropwise over 15 min. After stirring at -78^0C for 1 h, *N*-phenylbis(trifluoromethanesulfonimide) (2.5 g, 6.9 mmol) in dry THF (20 ml) was added over 10 min. The reaction was stirred at -78^0C for 1 h and then at 0^0C for 1 h before being quenched with saturated aqueous ammonium chloride (5 ml), diluted with water (300 ml) and extracted with ether (3x100 ml). The organic extracts were washed with water, brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography eluting with 5:1 ^{i}hexane/ether to afford a colourless foam (1.4 g).

^{1}H NMR ($CDCl_3$) 8.11 (1H, d, J = 8.8Hz), 7.75 (2H, d, J = 8.4Hz), 7.58 (1H, d, J = 1.4Hz), 7.30-7.23 (3H, m), 5.68 (1H, dd, J = 2.8, 6.7Hz), 4.17 (2H, q, J = 7.0Hz), 4.02 (1H, m), 3.00 (1H, septet, J = 7.1 Hz), 2.68-2.52 (4H, m), 2.37 (3H, s), 1.30 (6H, d, J = 7.0Hz), 1.27 (3H, t, J = 7.0Hz).

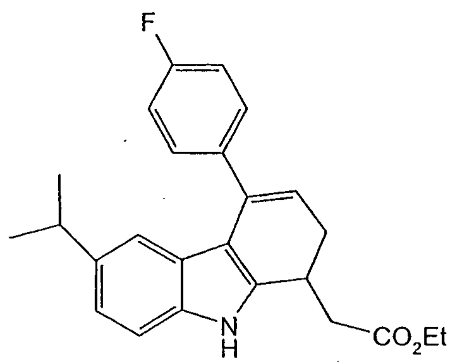
<u>Step 5</u>



To the product of Step 4 (500 mg, 0.83 mmol) in dioxane (25 ml) was added 4-fluorobenzeneboronic acid (128 mg, 0.91 mmol), potassium phosphate (264 mg, 1.2 mmol) and $Pd(PPh_3)_4$ (50 mg, 5 mol%). The mixture was heated at 80^0C for 3 h, allowed to cool, diluted with water (200 ml) and extracted with ethyl acetate (3x50 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated.

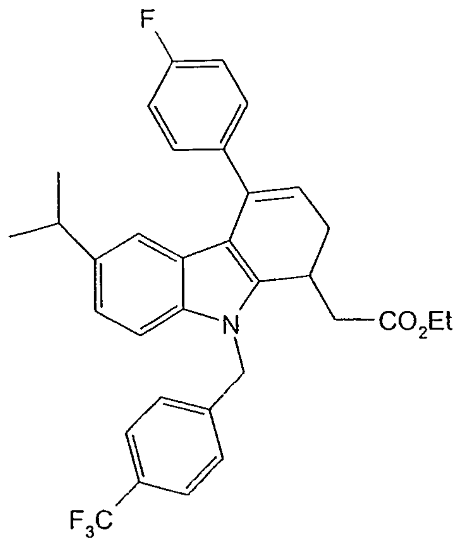
The product was purified by flash chromatography eluting with 9:1 ^{i}hexane/ethyl acetate to 5:1 ^{i}hexane/ethyl acetate to afford a colourless solid (395 mg).
m/z = 546 $[MH]^+$
^{1}H NMR ($CDCl_3$) 8.12 (1 H, d, J = 8.8Hz), 7.77 (2H, d, J = 8.4Hz), 7.43-7.22 (5H, m), 7.12-7.02 (2H, m), 6.43 (1H, d, J = 1.8Hz), 5.72 (1H, dd, J = 2.8, 6.7Hz), 4.19 (2 H, q, J = 7.1Hz), 4.13-4.06 (1H, m), 2.78-2.61 (4H, m), 2.54-2.47 (1 H, m), 2.35 (3 H, s), 1.27 (6 H, d, J=7.0Hz), 1.26 (3H, t, J = 7.0 Hz).

Step 6



The product of Step 5 (390 mg, 0.78 mmol) in a 1:1 mix of THF/methanol (10 ml) was treated with sodium dihydrogen phosphate (365 mg, 2.3 mmol) and sodium-mercury amalgam (5% sodium, 700 mg, excess). After stirring at room temperature for 2 h the reaction was decanted, diluted with water (100 ml) and extracted with ethyl acetate (3x50 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give a yellow oil (290 mg).
m/z = 378 $[MH]^+$

Step 7

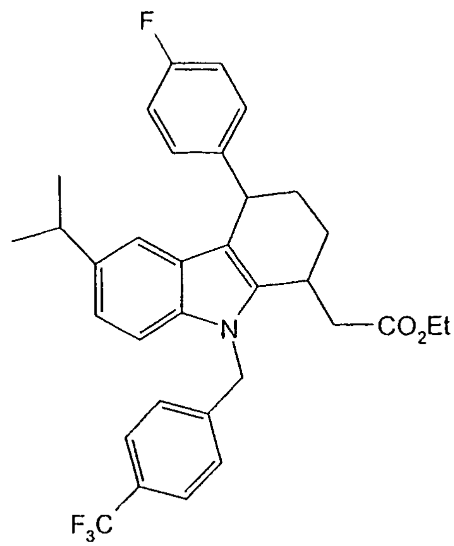


The product of Step 6 (200 mg, 0.5 mmol) in dry DMF (7 ml) was cooled to 0^0C under nitrogen, sodium hydride (60% dispersion in mineral oil, 25 mg, 0.55 mmol) was added, the reaction was stirred at 0^0C for 20 min, and then 4-(trifluoromethyl)benzyl bromide (350 mg, 0.6 mmol) was added. The reaction was allowed to warm to room temperature, stirred for 18 h, then diluted with water (100 ml) and extracted with ethyl acetate (3x50 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography eluting with 9:1 ^{i}hexane/ethyl acetate to 4:1 ^{i}hexane/ethyl acetate to afford a light green oil (180 mg).

^{1}H NMR ($CDCl_3$) 7.54 (2H, d, J = 8.4Hz), 7.48-7.43 (2H, m), 7.15-7.07 (5H, m), 7.00-6.97 (1H, m), 6.72 (1H, s), 5.58 (1 H, dd, J = 2.8, 6.7Hz), 5.56 (1H, d, J= 16Hz), 5.43 (1H, d, J = 16Hz), 3.61 (3 H, s), 3.41-3.34 (1H, m), 2.84-2.64 (3H, m), 2.54-2.47 (1H, m), 2.32 (1H, dd, J = 5.1, 16.0Hz), 1.10 (6H, d, J = 7.0Hz).

m/z =536 $[MH]^+$

Step 8



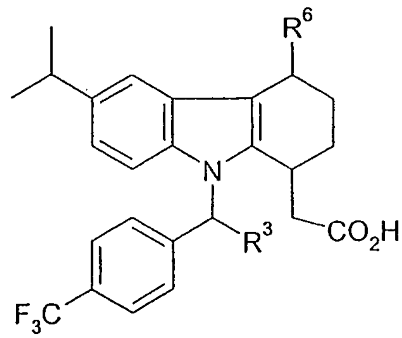
To the product of Step 7 (175 mg, 0.33 mmol) in ethyl acetate (25 ml) was added 10% palladium on carbon (25 mg). The mixture was shaken under an atmosphere of hydrogen at 50 psi for 36 h. The catalyst was removed by filtration, the filtrate evaporated, and the residue purified by flash chromatography eluting with 9:1 ^{i}hexane/ethyl acetate to 4:1 ^{i}hexane/ethyl acetate to give a colourless oil (155 mg). m/z =538 $[MH]^+$

Step 9

To the product from Step 8 (140 mg, 0.26 mmol) in THF (4 ml) was added lithium hydroxide (35 mg, 1.25 mmol) in water (1 ml). The reaction was stirred for 18 h and then diluted with water (100 ml), acidified with 2 M hydrochloric acid and extracted with ethyl acetate (3x50 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography eluting with 1:1 ^{i}hexane/ethyl acetate to ethyl acetate to give the title compound as a colourless solid (85 mg).

^{1}H NMR ($CDCl_3$) 7.54 (2H, d, J = 8.0Hz), 7.20-7.24 (2H, m), 7.10 (2H, d, J = 8.0Hz), 6.90-7.02 (4H, m), 6.52 (1 H, d, J = 1.4Hz), 5.39 (1H, d, J = 17 Hz), 5.32 (1H, d, J = 17Hz), 4.09-4.17 (1 H, m), 3.42 (1 H, t, J = 1.6Hz), 2.63-2.79 (2 H, m), 2.52-2.57 (1 H, m), 2.29-2.37 (1 H, m), 2.13-2.21 (2 H, m), 1.72-2.00 (2H, m), 1.05-1.29 (6 H, m). m/z =524 $[MH]^+$.

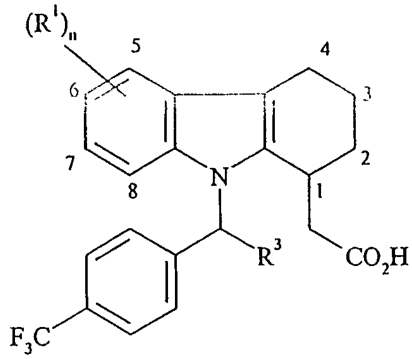
Following the same procedure, using the appropriate boronic acid in Step 5 and the appropriate benzyl halide in Step 7, there was prepared:



Example	R^3	R^6	mass spec $[MH]^+$
2a	n-propyl	4-F-Ph	566
2b	H	2,5-di-Me-Ph	534
2c	H	Ph	506
2d	H	4-MeO-Ph	536
2e	H	4-F-3-Me-Ph	538
2f	H	4-Cl-Ph	541
2g	H	3-F-Ph	-
2h	H	3,4-di-F-Ph	-
2i	H	3-pyridyl	507
2j	H	isopropyl	472

EXAMPLE 3

Following the procedure of Example 1, using the appropriate phenylhydrazine in Step 1 and the appropriate 1-(1-bromoalkyl)-4-trifluoromethylbenzene in Step 2, the following were prepared:



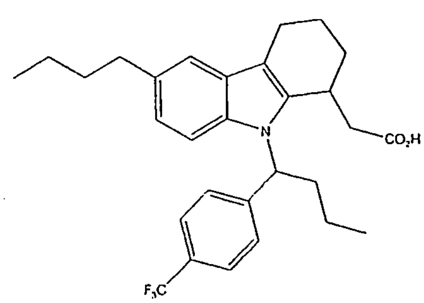
Example	$(R^1)_n$	R^3	mass spec*
3a	6-Br	n-propyl	508/510
3b	7-Br	n-propyl	508/510
3c	5-Br	n-propyl	508/510
3d	6-^{t}butyl	n-propyl	486
3e	6-OMe	n-propyl	460
3f	6-isopropoxy	n-propyl	-
3g	6-cyclohexyl	n-propyl	512
3h	6-isopropyl	ethyl	458
3i	6-isopropyl	n-propyl	472
3j	6,8-dichloro	ethyl	482, 484 (M-H)
3k	6,8-dichloro	n-propyl	498, 500
3l	5,7-dichloro	n-propyl	498, 500
3m	6-isopropyl	cyclohexyl	512
3n	6-isopropyl	isopropyl	472
3o	6-isopropyl	3-methylbutyl	500
3p	6-isopropyl	$CF_3CH_2CH_2$	526
3q	6-isopropyl	n-butyl	486
3r	H	n-propyl	428 (M-H)
3s	8-Cl-6-isopropyl	n-propyl	505 (M-H)
3t	5-bromo-8-fluoro	H	484 (M-H)
3u	5-bromo-8-chloro	H	478 (M-H)
3v	5,7-dimethyl	H	416

3w	8-bromo	H	464 (M-H)
3x	5-bromo	H	464 (M-H)
3y	7-bromo	H	464 (M-H)
3z	5-(3,4-di-Cl-Ph)-	H	532 (M-H)
3aa	6-chloro	n-propyl	464
3bb	6-isopropyl	2-methylpropyl	486
3cc	8-chloro	n-propyl	464
3dd	5,8-dichloro	H	-
3ee	8-n-butyl-6-isopropyl	H	486
3ff	8-cyclopropyl-6-isopropyl	H	470
3gg	8-isopropyl	H	430
3hh	5,7-dichloro	H	457
3ii	6,8-difluoro	n-propyl	466
3jj	8-ethyl	H	416
3kk	8-chloro	H	421
3ll	8-(3,4-di-Cl-Ph)-	H	532
3mm	6-isopropyl	allyl	488

* $[MH]^+$ unless otherwise indicated

EXAMPLE 4

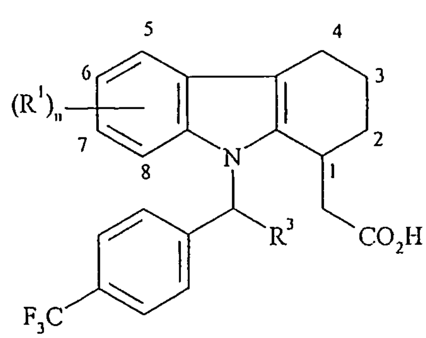
(6-Butyl-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid



To the product from Example 3a, Step 2 (55 mg, 0.1 mmol) in toluene (2 ml) and water (0.1 ml) were added butylboronic acid (15 mg, 0.134 mmol), potassium

phosphate (75 mg, 0.35 mmol), tricyclohexylphosphine (3 mg, 0.01 mmol) and palladium acetate (3 mg, 0.01 mmol). The mixture was degassed, placed under nitrogen and heated at 100^{0}C for 5h. After cooling the reaction was diluted with EtOAc (50 ml), passed through Celite and the filtrate washed with water (20 ml), brine (20 ml), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography eluting with ^{i}hexane to 20:1 ^{i}hexane/ether to give a colourless oil (25 mg) as a mix of diastereoisomers. To this ester (25 mg, 0.045 mmol) in THF (5 ml) under nitrogen was added a solution of lithium hydroxide (7 mg, 0.32 mmol) in water (1 ml). The reaction was stirred for 18 h and then diluted with water (30 ml), made acidic with hydrochloric acid (aqueous, 2 M) and extracted with EtOAc (3 x 20 ml). The organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography eluting with 4:1 ^{i}hexane/ethyl acetate to 1:1 ^{i}hexane/ethyl acetate to give (6-Butyl-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1- yl)acetic acid as a white solid (18 mg) as a 1:1 mix of diastereoisomers. ^{1}H NMR ($CDCl_3$) 7.54 (1H, J = 7.8 Hz), 7.48 (1H, J = 7.9 Hz), 7.24 (4H, m), 6.79 (1H, m), 5.41 (1H, t, J = 8.1 Hz), 3.50 (0.5 H, m, diastereomer A), 3.44 (0.5 H, m, diastereomer B), 2.82 (1H, m), 2.65 (3H, m), 2.52-2.45 (2H, m), 2.34-2.28 (1H, m), 2.0-1.76 (4H, m), 1.61 (2H, pent, J = 6.8 Hz), 1.41 –1.18 (5H, m), 0.99 – 0.71 (6H, m). m/z = 486 $[MH]^+$

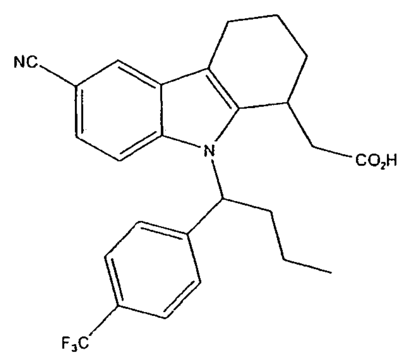
Following the same procedure, using the appropriate alkylboronic acid and using the intermediate from Step 2 of Example 3a, 3b or 3c as appropriate, there was also prepared:



Example	$(R^1)_n$	R^3	mass spec
4a	6-cyclopropyl	n-propyl	470
4b	6-(2-methylpropyl)	n-propyl	486
4c	5-cyclopropyl	n-propyl	468 (M-H)
4d	5-isopropyl	n-propyl	472
4e	7-cyclopropyl	n-propyl	468 (M-H)

EXAMPLE 5

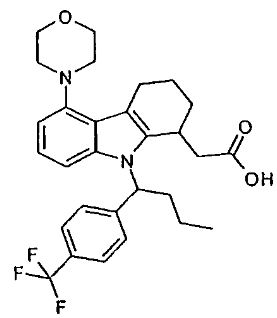
(6-Cyano-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid



To the intermediate from Example 3a, Step 2 (85 mg, 0.16 mmol) in dry *N*-methyl-2-pyrrolidinone (5 ml) under nitrogen was added copper (I) cyanide (50 mg, 0.56 mmol). The mixture was heated at 180^0C for 3 h. After cooling the reaction was diluted with water (50 ml) and extracted with diethyl ether (3 x 20 ml). The ether extracts were washed with aqueous ammonia solution (3 x 20 ml), water (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography eluting with 9:1 ^{i}hexane/ether to 4:1 ^{i}hexane/ether to give a white solid (68 mg). The ester was hydrolysed as in Example 1, step 3 to give the title compound as a white solid (55 mg) as a ca. 1:1 mix of diastereoisomers. ^{1}H NMR ($CDCl_3$) 7.85 (1H, d, J = 12.1 Hz), 7.59-7.51 (2H, m), 7.30-7.16 (3.5H, m), 6.86 (0.5H, d, J = 7.1 Hz), 5.48 (1H, t, J = 7.4 Hz), 3.59-3.49 (0.5H, m, diastereomerA), 3.47-3.39 (0.5H, m, diastereomer B), 2.91-2.75 (1H, m), 2.71-2.39 (3H, m), 2.01-1.95 (2H, m), 1.91-1.81 (2H, m), 1.33-1.18 (2H, m), 0.97 (2H, m), 0.85 (3H, t, J = 7.1 Hz). m/z = 455 $[MH]^+$

EXAMPLE 6

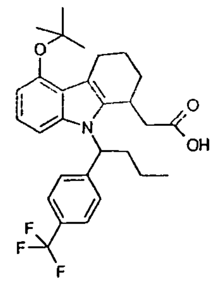
(5-(morpholin-1-yl)-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid



Potassium hydroxide (20 mg), cetyltrimethylammonium bromide (4mg) and bis(tri t-butylphosphino)palladium(0) (2mg) were mixed and the flask purged with nitrogen. The product from Example 3c, Step 2 (144mg) was dissolved in toluene (1.5ml) and added followed by morpholine (17μL) and water (5 μL) and the mixture heated at 90°C for 15hrs. The reaction was cooled to ambient temperature, water added and the mixture extracted with ethyl acetate (x3). The combined organics were washed with brine, evaporated in vacuo and purified by chromatography (Silica gel and 20:1 hexane:ethyl acetate) to give the desired ethyl (5-(morpholin-1-yl)-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetate as a mixture of diastereoisomers.(10mg). MH+ 543. This ester was hydrolysed using the procedure of example 1, step 3 to afford the desired (5-(morpholin-1-yl)-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid (8mg) as a mixture of diastereoisomers ^{1}H NMR δ ppm ($CDCl_3$) 7.56 (1H, d, J= 8.4Hz), 7.52 (1H, d, J=8.2 Hz), 7.26 (0.5H, m), 7.18 (1H, d, J=7.85Hz), 7.14 (1H, d, J=8.25Hz), 7.01 (0.5H, t, J=7.95Hz), 6.85-6.97 (1.5H, m), 6.74 (0.5H, d, J=8.05), 5.40-5.55 (1H, m), 4.09 (4H, br s), 3.15-3.6 (5.5H, m), 2.78-2.95 (1H,m), 2.33-2.75 (4H, m), 1.70-2.10 (4H, m), 1.45-1.60 (0.5H, m), 1.15-1.40 (1.5H, m), 0.99 (1.5H, t, J=7.3Hz), 0.88 (1.5H, t, J=7.3Hz), 0.7-0.83 (0.5H, m). m/z 513 [MH+]

EXAMPLE 7

(5-(tert-Butyloxy)-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid

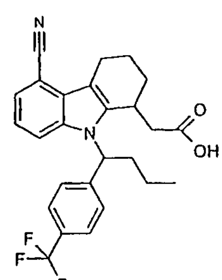


To a mixture of palladium acetate (2.6mg), 2-(di-t-butylphosphino)biphenyl (2mg) and sodium t-butoxide (27mg) in a nitrogen-purged flask was added toluene (0.5ml) and the product from Example 3c, Step 2 (99mg) as a solution in toluene (1ml). The reaction was heated at 100°C for 3hrs, cooled, water added and the mixture extracted with ethyl acetate (x2). The combined organic extracts were dried over $MgSO_4$, evaporated in vacuo and purified by chromatography using silica gel / 20:1 hexane: ethyl acetate to give the desired ethyl (5-(tert-butyloxy)-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetate (70mg). This ester was hydrolysed using the procedure of Example 1, Step 3 to afford the desired (5-(tert-butyloxy)-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid (50mg)

^{1}H NMR ($CDCl_3$) 7.45-7.60 (3H, m), 7.31 (1H, d, J=8.2Hz), 7.18 (1H, d, J=8.0), 6.95-7.1 (2H, m), 5.45 (1H, br s), 3.51 (0.5H, d, J=15Hz), 3.41 (0.5H, d, J=10Hz), 2.80-2.90 (1H, m), 2.25-2.75 (7H, m), 1.80-2.03 (4H, m), 1.15-1.60 (9H, m), 0.99 (1.5H, t, J=7.5Hz), 0.80-0.90 (1.5H, m)

EXAMPLE 8

(5-Cyano-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid

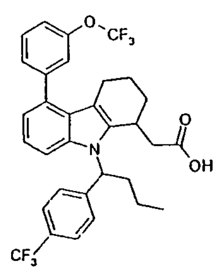


Prepared from the intermediate from Example 3c, Step 2 (100mg) using the method of Example 5 to give desired compound as a mixture of diastereoisomers (35mg) ^{1}H

NMR δ ppm ($CDCl_3$) 7.57 (1H, d, J=8Hz), 7.53 (1H, d, J=15Hz), 7.35-7.45 (1H, m), 7.26 (1H, d, J=6Hz), 7.16 (1H, d, J=8Hz), 6.95-7.10 (2H, m), 5.5 (1H s), 3.4-3.6 (1H, m), 3.20-3.40 (1H, m), 2.80-3.0 (1H, m), 2.30-2.80 (4H, m), 2.17 (0.5H, s), 1.80-2.10 (4H, m), 1.45-1.60 (0.5H, m), 1.43 (0.5H, s), 1.15-1.35 (1H, m), 1.00 (1.5H, t, J=7.3Hz), 0.88 (2.0H, m). m/z = 453 [M-H]

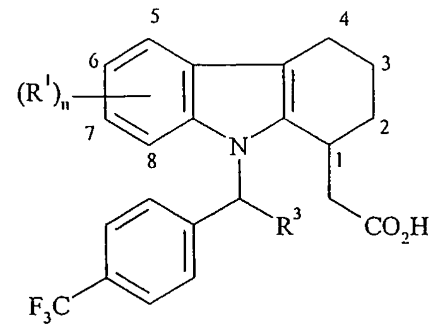
EXAMPLE 9

(5-(3-{trifluoromethoxy}phenyl)-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid



The intermediate from Example 3c, Step 2 (733mg) was dissolved in THF (80ml) under nitrogen and 3-trifluoromethoxyphenyl boronic acid (383mg) was added followed by potassium carbonate (290mg) as a solution in water (18ml). Finally, $Pd(PPh_3)_4$ (78mg) was added and the reaction heated at 85°C for 15hrs. Water was added and the mixture extracted with ethyl acetate. The organic phase was washed with brine, evaporated and purified by chromatography (silica gel / 20:1 hexane : ethyl acetate) to yield the desired ester (700mg) which was hydrolysed using the procedure of example 1, step 3 to afford the desired (5-(3-{trifluoromethoxy}phenyl)-9-{1-[4-(trifluoromethyl)phenyl] propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid which was separated into single isomers by supercritical fluid chromatography. Diastereoisomer A: ^{1}H NMR δ ppm ($CDCl_3$) 7.57 (2H, d, J=8.3Hz), 7.37-7.45 (2H, m), 7.38 (2H, d, J=8.3), 7.23 (1H, d, J=8), 6.98 (1H, t, J=7.5Hz), 6.91 (1H, d, J=6.7Hz), 6.84 (1H, d, J=8Hz), 5.48 (1H, dd, J=3.5,11Hz), 3.51 (1H, d, J=9.5Hz), 1.50-2.60 (13H, m), 0.91 (3H, d, J=7Hz). Diastereoisomer B: ^{1}H NMR δ ppm ($CDCl_3$) 7.42-7.65 (5H, m), 7.15-7.40 (3H, m), 7.06 (1H, t, J=9Hz), 6.89 (1H, d, J=9Hz), 5.49 (1H, br s), 3.45 (1H, br s), 1.25-2.80 (13H, m) 1.02 (3H, t, J=9Hz)

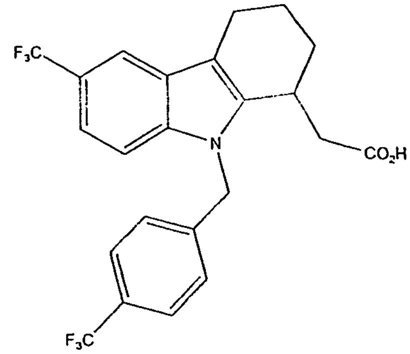
Following analogous procedures, using the appropriate boronic acid and using the intermediate from Step 2 of Example 3a, 3b or 3c as appropriate, the following were prepared:



Example	$(R^1)_n$	R^3	mass spec
9a	5-(3,4-di-Cl-Ph)	n-propyl	574
9b	5-(3,4-di-Cl-Ph)	ethyl	560
9c	5-(3,4-di-Cl-Ph)	H	532
9d	5-(3-MeS-Ph)	H	510
9e	6-(3,4-di-Cl-Ph)	n-propyl	574
9f	5-(2,5-di-Me-Ph)	H	492
9g	7-(3,4-di-Cl-Ph)	H	530 (M-H)
9h	7-(3-pyridyl)	H	465
9i	7-(3-thienyl)	H	-
9j	7-(2,5-di-Me-Ph)	H	492

EXAMPLE 10

(6-Trifluoromethyl-9-{4-(trifluoromethyl)benzyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid



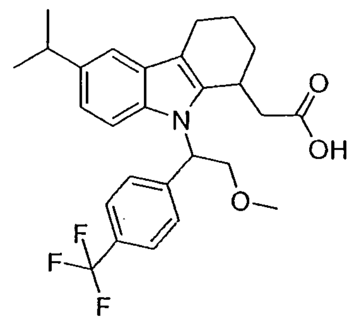
To a mixture of iodine (3.9 g, 15.5 mmol) and silver sulfate (4.8 g, 15.5 mmol) in ethanol (150 ml) was added 4-trifluoromethylaniline (2.5 g, 15.5 mmol). The mixture was stirred for 2 h, filtered, the solids washed well with EtOAc and the filtrate concentrated *in vacuo*. The residue was take up in DCM (100 ml) washed with 5% aqueous sodium hydroxide (50 ml), water (40 ml), brine (30 ml), dried ($MgSO_4$), filtered and evaporated. The crude 2-iodo-4-trifluoromethylaniline was purified by flash chromatography eluting with 4:1 ^{i}hexane/DCM to give an orange solid (3.1 g). To the 2-iodo-4-trifluoromethylaniline from the foregoing step (900 mg, 3.14 mmol) in dry DMF (2 ml) were added ethyl 2-cyclohexanoneacetate (0.62 ml, 3. 5 mmol), *p*-toluenesulfonic acid (20 mg), and tetraethoxysilane (0.9 ml, 4.1 mmol). The mixture was heated at 130^{0}C for 5 h, allowed to cool to 110^{0}C and more DMF (5 ml) was added followed by Hunig's base (2 ml) and palladium acetate (30 mg, 5 mol%). Reaction heated at 110^{0}C for 15 h. After cooling, the reaction was diluted with EtOAc (100 ml), washed with water (2 x 30 ml), 2M aqueous HCl (30 ml), brine (30 ml), dried ($MgSO_4$), filtered and evaporated. The crude ethyl ({6-trifluoromethyl}-2,3,4,9-tetrahydro-1-carbazol-1-yl)acetate was purified by flash chromatography eluting with ^{i}hexane to 10:1 ^{i}hexane/ether to give a yellow oil (260 mg) which was benzylated under the conditions of Example 1, Step 2. The resultant ethyl (6-trifluoromethyl-9-{4-(trifluoromethyl)benzyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetate was hydrolysed using the procedure of Example 1, Step 3 to give the desired (6-trifluoromethyl-9-{4-(trifluoromethyl)benzyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid a white solid (40 mg).

^{1}H NMR (MeOD) 7.76 (1H, s), 7.55 (2H, d, J = 8.2 Hz), 7.32 (2H, m), 7.07 (2H, d, J = 8.2 Hz), 5.58 (1H, d, J=17.7 Hz,), 5.48 (1H, d, J= 17.7 Hz), 3.31 (1H, m), 2.92-2.81 (1H, m), 2.72-2.62 (1H, m), 2.48 (2H, m), 1.99-1.81 (4H, m).

m/z = 456 $[MH]^+$

EXAMPLE 11

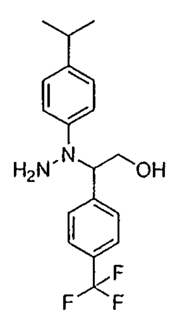
(6-isopropyl-9-{2-methoxy-1-[4-(trifluoromethyl)phenyl]ethyl}-2,3,4,9-tetrahydro-1H-carbazol-1-yl)acetic acid



Step 1 2-bromo-2-[4-(trifluoromethyl)phenyl]ethanol

[4-(trifluoromethyl)phenyl]oxirane (980 mg, 5.27 mmol) (prepared according to J. Med. Chem. 2002, 45 (18), 3891) was dissolved in $CHCl_3$ (20 ml), HBr (48% aq, 15 ml) was added and the mixture stirred at room temperature for 3 hours. The organic layer was separated, washed with $NaHCO_3$ solution (20 ml) and with brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to yield 1.2 g (86%) of the title compound: δ_H (360 MHz, $CDCl_3$) 7.64 (2 H, d, J = 8.3 Hz), 7.56 (2 H, d, J = 8.3 Hz), 5.07 (1 H, dd, J = 5.8, 7.4 Hz), 4.12-3.96 (2 H, m), 2.13 (1 H, m).

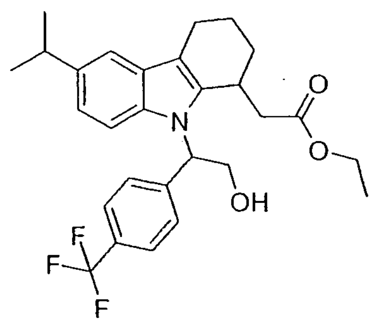
Step 2 2-[1-(4-isopropylphenyl)hydrazino]-2-[4-(trifluoromethyl) phenyl]ethanol



(4-Isopropylphenyl)hydrazine hydrochloride (450 mg, 2.4 mmol) was suspended in toluene (10 ml), Et_3N (0.43 ml, 3.1 mmol) was added and the mixture refluxed for 1 hour and then cooled to room temperature. 2-Bromo-2-[4-(trifluoromethyl)phenyl]ethanol from the foregoing step (0.48 g, 1.8 mmol) in toluene (2 ml) was added and the solution was heated to 80^0C for 5 hours. After cooling to

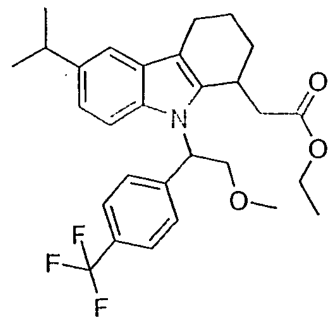
room temperature the white solid formed during the reaction was filtered and the solution concentrated. Purification by chromatography on silica gel eluting with a gradient 10-50% ethyl acetate/ hexane afforded 330 mg of the title compound (40%): δ (360 MHz, $CDCl_3$): 7.55 (2 H, d, J = 8.3 Hz), 7.38 (2 H, d, J = 8.3 Hz), 7.13-7.09 (2 H, m), 6.86-6.82 (2 H, m), 4.82 (1 H, dd, J = 3.4, 7.8 Hz), 4.27 (1 H, dd, J = 7.8, 11.5 Hz), 4.01 (1 H, dd, J = 3.4, 11.5 Hz), 3.73 (2 H, s), 2.85-2.77 (1 H, septet, J = 6.9), 1.19 (6 H, d, J = 6.9), *m/z* (ES^+) 339 (MH^+), 322 ($M-NH_2^+$).

<u>Step 3 Ethyl (9-{2-hydroxy-1-[4-(trifluoromethyl)phenyl]ethyl}-6-isopropyl-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetate</u>



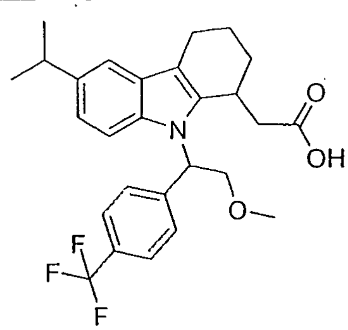
2-[1-(4-Isopropylphenyl)hydrazine]-2-[4-(trifluoromethyl) phenyl] ethanol from the foregoing step (1.0 g, 2.96 mmol) was dissolved in ethanol (20 ml) and ethyl (2-oxocyclohexyl)acetate (0.53 ml, 2.96 mmol) and p-toluenesulphonic acid monohydrate (1.12 g, 5.97 mmol) added and the reaction mixture refluxed under nitrogen overnight. The solvent was then concentrated *in vacuo* and the residue was purified by chromatography on silica gel eluting with 20% ethyl acetate/ hexane to give 970 mg of the title compound (67%) as a 1:1 mixture of diastereoisomers: *m/z* (ES^+) 488 (MH^+).

<u>Step 4 Ethyl (6-isopropyl-9-{2-methoxy-1-[4-(trifluoromethyl) phenyl]ethyl}-2,3,4,9-tetrahydro-1H-carbazol-1-yl)acetate</u>



Ethyl (9-{2-hydroxy-1-[4-(trifluoromethyl)phenyl]ethyl}-6-isopropyl-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetate from the foregoing step (100 mg, 0.2 mmol; 1:1 mixture of diasteroisomers) was dissolved in DMF (5 ml) and cooled to 0^0C. NaH (60% dispersion in oil, 9 mg, 0.2 mmol) was added and the mixture stirred at 0^0C for 30 minutes. Then MeI (38 µl, 0.6 mmol) was added and the mixture slowly warmed to room temperature. After stirring for 30 minutes at room temperature, H_2O (10 ml) and ethyl acetate (20 ml) were added, the layers separated and the organic dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica gel eluting with 50% ethyl acetate/ hexane afforded 47 mg of the title compound (47%) as a 3:2 mixture of diasteroisomers.

Step 5 (6-isopropyl-9-{2-methoxy-1-[4-(trifluoro methyl)phenyl]ethyl}-2,3,4,9-tetrahydro-1H-carbazol-1-yl)acetic acid

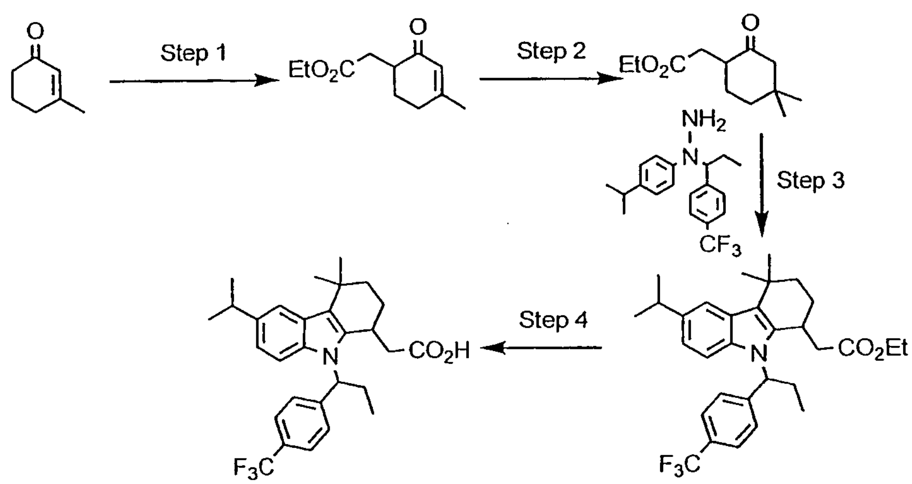


Ethyl (6-isopropyl-9-{2-methoxy-1-[4-(trifluoromethyl)phenyl]ethyl}-2,3,4,9-tetrahydro-1H-carbazol-1-yl)acetate from the foregoing step (46 mg, 0.092 mmol; 3:2 mixture of diasteroisomers) was dissolved in THF (2 ml) and LiOH (22 mg, 0.92 mmol) in H_2O (1 ml) added. The reaction mixture was stirred heating to 50^0C for 12 hours. It was then diluted with ethyl acetate (20 ml), washed with 1 N HCl (20 ml), brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica gel eluting with 50% ethyl acetate/ hexane and then with

50% ethyl acetate/ hexane + 0.1% acetic acid followed by a further purification with preparative HPLC (gradient 30-85% CH_3CN-0.1%TFA/H_2O) afforded 27 mg of the desired (6-isopropyl-9-{2-methoxy-1-[4-(trifluoromethyl)phenyl]ethyl}-2,3,4,9-tetrahydro-1H-carbazol-1-yl)acetic acid (67%) as a 1:1 mixture of diasteroisomers (a+b): δ (360 MHz, $CDCl_3$) 7.56 (1 H, d, J = 8.2 Hz, a/b), 7.50 (1 H, d, J = 8.1 Hz, a/b), 7.41 (1 H, d, J = 8.2 Hz, a/b), 7.32 (1 H, m, a+b), 7.20 (1 H, d, J = 8.2 Hz, a/b), 6.86 (1.5 H, m, a+b), 6.77 (0.5 H, d, J = 8.5 Hz, a/b), 5.66-5.61 (1 H, m, a+b), 4.44 (0.5 H, dd, J = 6.0, 9.7 Hz, a/b), 4.33-4.25 (1 H, m, a/b), 3.97 (0.5 H, dd, J = 6.2, 9.8 Hz, a/b), 3.55 (0.5 H, br d, a/b), 3.45 (0.5 H, br d, a/b), 3.37 (1.5 H, s, a/b), 3.31 (1.5 H, s, a/b), 3.05-2.84 (2.5 H, m, a+b), 2.72-2.39 (2.5H, m, a+b), 1.99-1.85 (4H, m, a+b) 1.27 (6 H, dd, J = 4.1, 6.8 Hz, a+b); *m/z* (ES^+) 474 (MH^+).

EXAMPLE 12

(6-Isopropyl-4,4-dimethyl-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1- yl)acetic acid



Step 1 Ethyl (4-methyl-2-oxocyclohex-3-en-1-yl)acetate

A solution of 3-methyl-2-cyclohexen-1-one (3.0g, 27.23mmol) in THF (10ml) was added dropwise into a stirring solution of LDA (1.5M in THF, 19.97ml) in THF (10ml) at -78^{0}C. After stirring for 30min at -78^{0}C, a solution of ethyl bromoacetate (3.34ml, 29.96mmol) in THF (10ml) was added dropwise. After addition, stirring was continued at ambient temperature for 2hrs. The reaction mixture was quenched with HCl (2N, 100ml) and the mixture was extracted with ethyl acetate (2×100ml). The organic extract was washed with brine (1×100ml), dried over $MgSO_4$ and concentrated

in vacuo. The residue was purified by flash chromatography eluting with 20% ethyl acetate in hexane to afford (4-methyl-2-oxocyclohex-3-en-1-yl)acetate as a yellow oil (3.76g, 70%).1H NMR δ (ppm)(360MHz, CDCl3): 5.88 (1 H, s), 4.19-4.11 (2 H, m), 2.89 (1 H, dd, J = 5.3, 16.2 Hz), 2.79-2.71 (1 H, m), 2.46-2.22 (3 H, m), 2.14-2.04 (1 H, m), 1.96 (3 H, s), 1.84-1.76 (1 H, m), 1.32-1.24 (3 H, m).

Step 2 Ethyl (4,4-dimethyl-2-oxocyclohexyl)acetate

Copper iodide (225mg, 1.18mmol) was added into a solution of methylmagnesium iodide (3.39ml, 3M in THF, 10.19mmol) in ether (10ml) at -5^{0}C. The resulting mixture was stirred for 30 min and then enone from the foregoing step (2.0g, 10.19mmol) in ether (10ml) was added dropwise. The reaction mixture was stirred at -5^{0}C for 2hrs and then at ambient temperature for 1hr. The reaction mixture was quenched with sat. ammonium chloride (100ml) and extracted with ether (3×100ml). The organic extract was washed with brine (1×100ml), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by gradient flash chromatography eluting with1% to 2% ethyl acetate in hexane to afford ethyl (4,4-dimethyl-2-oxocyclohexyl)acetate as an oil (695mg, 32%).1H NMR δ (ppm)(400MHz, CDCl3): 4.16-4.09 (2 H, m), 2.80-2.70 (2 H, m), 2.30 (1 H, d, J = 13Hz), 2.18-2.11 (2 H, m), 2.05-1.99 (1 H, m), 1.74-1.55 (3 H, m), 1.26 (3 H, t, J = 7.1Hz), 1.08 (3 H, s), 0.87 (3 H, s).

Step 3 Ethyl (6-isopropyl-4,4-dimethyl-9-{1-[4-(trifluoromethyl) phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1- yl)acetate

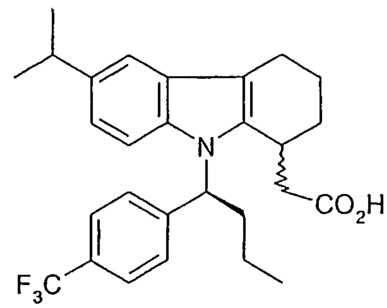
A mixture of ethyl (4,4-dimethyl-2-oxocyclohexyl)acetate from the foregoing step (200mg, 0.94mmol), 1-(4-isopropylphenyl)-1-{1-[4-(trifluoromethyl)phenyl] propyl} hydrazine (prepared from ethyl magnesium chloride and 4-trifluoromethylbenzaldehyde using the procedure of Example 13, Step 1 followed by treatment with carbon tetrabromide/triphenyl phosphine using the procedure of Example 13, Step 4 and finally treatment with 4-isopropylphenyl hydrazine hydrochloride using the procedure of Example 13, Step 5) (317mg, 0.94mmol) and PTSA (360mg, 1.88mmol) in ethanol (30ml) was refluxed for 18hrs. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue

was diluted with ethyl acetate (100ml) and sequentially washed with water (1× 100ml), hydrochloric acid (2N, 100ml) and brine (100ml). The organic extract was dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography eluting with 2% ethyl acetate in hexane to afford the desired product (ethyl (6-isopropyl-4,4-dimethyl-9-{1-[4-(trifluoromethyl) phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1- yl)acetate) as a mixture of two diastereoisomers A & B (2:1) (112mg, 23%). 1H NMR (360MHz, $CDCl_3$) δ: 7.54-7.42 (8 H, m, diast A+B), 7.20-7.18 (1 H, m, diast A), 7.12-7.08 (1 H, m, diast B), 7.02-6.88 (1 H, m, diast A), 6.90-6.88 (1 H, m, diast B) 6.82-6.78 (1 H, m, diast A), 6.70-6.67 (1 H, m, diast B), 5.42-5.34 (2 H, m, diast A+B), 4.19-4.08 (4 H, m, diast A+B), 3.52-3.44 (1 H, m, diast B), 3.38-3.32 (1 H, m, diast A) 3.06-2.92 (2 H, m, diast A+B), 2.71-2.42 (8 H, m, diast A+B), 1.88-1.72 (4 H, m, diast A+B), 1.64-1.52 (8 H, m, diast A+B), 1.40-1.02 (20 H, m, diast A+B), 0.90-0.80 (12 H, m, diast A+B) ppm

Step 4 (6-Isopropyl-4,4-dimethyl-9-{1-[4-(trifluoromethyl) phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1- yl)acetic acid

A solution of lithium hydroxide (52mg, 2.2mmol) in water (2ml) was added into a solution of ethyl (6-isopropyl-4,4-dimethyl-9-{1-[4-(trifluoromethyl)phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1- yl)acetate from the foregoing step (110mg, 0.22mmol) in dioxane (4ml) and stirred at 60^0C for 18hrs. The reaction mixture was diluted with hydrochloric acid (2N, 20ml) and extracted with ethyl acetate (2×50ml). The organic extract was washed with brine (1×50ml), dried over $MgSO_4$ and concentrated in vacuo, to afford (6-isopropyl-4,4-dimethyl-9-{1-[4-(trifluoromethyl) phenyl]propyl}-2,3,4,9-tetrahydro-1 H -carbazol-1- yl)acetic acid as a mixture of two diastereoisomers A & B (2:1) (10mg, 10%) 1H NMR (400MHz, $CDCl_3$) δ:7.57-7.50 (4 H, m, diast A+B), 7.35 (1 H, d, J = 8.0Hz, diast A), 7.18 (1 H, d, J = 8.0Hz, diast A), 7.12 (1 H, d, J = 8.5Hz, diast B), 6.91 (1 H, d, 8.4Hz, diast A), 6.83 (1 H, d, J = 8.5Hz, diast B), 6.70 (1 H, d, J = 8.4Hz, diast B), 5.36-5.30 (2 H, m, diast A+B), 3.49-3.42 (1 H, m, diast B), 3.40-3.31 (1 H, m, diast A), 3.01-2.94 (2 H, m, diast A+B), 2.72-2.41 (8 H, m, diast A+B), 1.86-1.80 (4 H, m, diast A+B), 1.54-1.58 (2 H, m, diast A+B), 1.54-1.52 (6 H, m, diast A+B), 1.36-1.41 (6 H, m, diast A+B)1.22-1.29 (12 H, m, diast A+B), 1.01-1.08 (4 H, m, diast A+B), 0.82-0.91 (6 H, m, diast A+B) ppm.

EXAMPLE 13



Step 1

To a solution of 4-trifluoromethylbenzaldehyde (9.7g, 56mmol.) in THF (100ml) at 0°C was added n-propyl magnesium chloride (31ml of 2M solution in ether, 61mmol.) over 5mins. At the end of addition, the solution was stirred 10 minutes at 0°C then warmed to rt for 1 hour and quenched by the addition of a saturated aqueous solution of ammonium chloride (50ml). This was extracted with ether (2x100ml) and the combined organics washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (silica; eluant 5%EtOAc:hexane) to yield (RS)-1-(4-trifluoromethylphenyl)butan-1-ol as a pale yellow oil (4.7g).

Step 2

The alcohol from the foregoing step (4.7g, 21.4mmol.) in acetone (100ml) and cooled to 0°C under nitrogen was treated with Jones reagent (7.5ml) (from a stock of CrO_3 [40g] in water [80ml]/conc. H_2SO_4 [20ml]) portionwise over 10 minutes and the resultant green mixture stirred a further 30 minutes at 0°C. The reaction was diluted with water and extracted with ether (2x100ml). The combined organics were washed with water (3x100ml), dried ($MgSO_4$) and evaporated. The residue was purified by filtration through a plug of silica (eluant hexane) to yield 1-(4-trifluoromethylphenyl)butan-1-one as a colourless liquid (4.1g).

Step 3

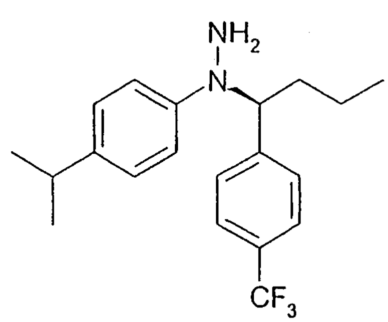
To a pre-cooled (-30°C) solution of borane.dimethylsulfide complex (3.1ml, 32.4mmol.) in toluene (30ml) was added (R)-methyl CBS oxazaborolidine (1M

solution in toluene, 3.3ml, 3.3mmol.) and the mixture stirred 15 minutes at -30°C. The ketone from the foregoing step (7.0g, 32.4mmol.) as a solution in a mixture of dichloromethane (30ml) and toluene (30ml) was added dropwise over 30 minutes and the reaction stirred a further 6h at -30°C. The reaction was quenched by the cautious addition of methanol (7ml) and the mixture diluted with ether and 1N HCl (50ml). The organic layer was separated and washed with further 1N HCl (50ml) and brine, dried ($MgSO_4$) and evaporated. The residual liquid was purified by chromatography (silica; eluent 5%EtOAc:hexane) to yield (S)-1-(4-trifluoromethylphenyl)-butan-1-ol as a colourless oil (5.22g) which solidified on standing. Derivatization of a sample as its Mosher's ester (MTPACl, Et_3N, DMAP, DCM, rt, 30mins) showed the ee to be 91%.

Step 4

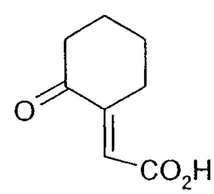
To a stirred solution of (S)-1-(4-trifluoromethylphenyl)-butan-1-ol from the foregoing step (4.65g, 21mmol., 91%ee) in dry dichloromethane (100ml) cooled to 0°C was added a $MgSO_4$-dried solution of carbon tetrabromide (9.91g, 1.4 eq.) in dry dichloromethane (50ml). Triphenylphosphine (8.38g, 1.5eq.) was then added portionwise over 20 minutes maintaining internal temperature below 6°C. The cooling bath was removed at the end of the addition and the reaction stirred for 30 minutes, reduced to ca. half volume in vacuo and the remaining solution applied to a pad of silica gel and eluted with ether. The combined ether fractions containing product were evaporated in vacuo and the residue purified by flash chromatography (silica; eluant hexane) to yield 5.1g (R)-1-(4-trifluoromethylphenyl)-1-bromobutane.

Step 5



To a stirred suspension of 4-isopropylphenylhydrazine hydrochloride (545mg, 2.8mmol.) in dry THF (20ml) cooled to 0°C was added a solution of NaHMDS (5.9ml of a 1M solution in THF, 2.1eq.). The cooling bath was removed and the yellow suspension stirred for 1 hour then recooled to 0°C. The bromide from the foregoing step (820mg, 2.9mmol.) as a solution in dry THF (10ml) was added, the cooling bath removed and the mixture stirred at ambient temperature for 17 hours. The reaction was diluted with ether (150ml) and water (100ml) and the layers separated. The aqueous was further extracted with ether (100ml) and the combined ether layers washed with water (2x100ml) and brine (100ml), dried ($MgSO_4$) and evaporated to give 1.3g of a deep red oil. Purification by column chromatography (silica; eluant 10% ethyl acetate : hexane) gave the product (530mg) as a red oil. (86% ee by chiral HPLC)

Step 6



To a solution of sodium methoxide in methanol (25%, 117ml, 0.51mole) at 5°C was added a mixture of cyclohexanone (50g, 1eq.) and diethyl oxalate (70ml, 1eq.) and the mixture stirred at room temperature for 6 hours. The reaction was quenched by the addition of water (1500ml) and EtOAc (1000ml) and the aqueous layer separated and acidified with conc. HCl and extracted with further EtOAc (2x1000ml). The combined organics were dried ($MgSO_4$) and evaporated in vacuo to give 90g of crude intermediate which was used directly in the next step.
The crude ketoester from the foregoing step was added to a mixture of aqueous potassium dihydrogen phosphate (770ml of 1M solution), aqueous sodium hydrogen phosphate (1700ml of 0.5M solution) and 50% aqueous glyoxylic acid (188ml) at 5°C. The mixture was adjusted to pH 6-7 with conc. NaOH solution then stirred at 5°C for 1 hour before being washed with EtOAc (500ml). The aqueous layer was acidified with conc. HCl then extracted with EtOAc (2x700ml) and the combined organics

dried ($MgSO_4$) and evaporated in vacuo to give a residue which was triturated with heptane to yield the desired product as a pale yellow, gummy solid (37g).

Step 7 (Fischer indole synthesis)

To a stirred solution of the hydrazine from Step 5 (556mg, 1.59mmol.) in dry isopropanol (20ml) was added p-toluenesulfonic acid monohydrate (271mg, 0.9eq.), the product from Step 6 (489mg, 2eq.) and powdered 3A molecular sieves (600mg) and the resulting mixture heated to gentle reflux for 3 hours. The reaction was cooled, diluted with water (50ml) and extracted into EtOAc (2x100ml). The combined organics were washed with 1N HCl (100ml) and brine (100ml), dried ($MgSO_4$) and evaporated in vacuo to leave a residue which was purified by chromatography (silica; eluant 1:2 ethyl acetate:hexane) to give the product (460mg) as a yellow foam.

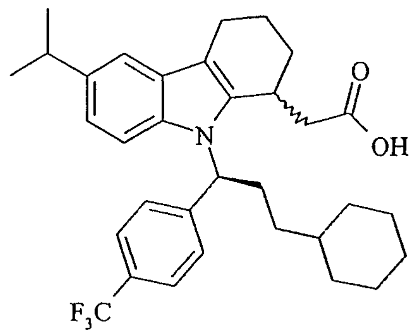
Step 8 – Asymmetric hydrogenation

To a stirred solution of the product from the foregoing step (460mg, 0.98mmol.) in methanol (25ml) in a thick-walled flask was added triethylamine (0.14ml, 1.0eq.) and the solution degassed by nitrogen bubbling for 10 minutes. (S)-Ru(BINAP)Cl_2 (78mg, 10mol%) was added and the mixture placed under an atmosphere of hydrogen (35psi), warmed to 40°C and shaken under hydrogen for 14 hours. The mixture was cooled, diluted with EtOAc (100ml) and washed with 1N HCl (50ml). The aqueous layer was extracted with further EtOAc (100ml) and the combined organics washed with brine (50ml) and dried ($MgSO_4$). To the resulting yellow solution was added activated charcoal (1g), the suspension stirred 10 minutes and then filtered through a pad of Celite™ washing well with further EtOAc. The filtrate was evaporated to give a residue which was purified by chromatography (silica; eluant 1:2 ethyl acetate:hexane) to give the product (320mg) as a pale brown foam (87:13 mix of diastereomers). This diastereomeric mixture could be crystallized to purity via its dicyclohexylamine salt.

1H NMR (free acid) δ (ppm)(500MHz, $CDCl_3$): 7.54 (2H, d, J 8.0Hz), 7.33-7.31 (3H, m), 6.87 (1H, dd, J 8.5, 1.5Hz), 6.76 (1H, d, J 8.5Hz), 5.40 (1H, dd, J 10.5, 4.0Hz), 3.48 (1H, m), 2.96 (1H, septet, J 7.0Hz), 2.86 (1H, dd, J = 15.0, 4.0 Hz), 2.68 (1H, m),

2.52-2.44 (2H, m), 2.37-2.30 (2H, m), 1.96 (3H, m), 1.85-1.81 (1H, m), 1.28 (6H, d, J 7.0Hz), 1.21 (1H, m) and 0.87 (4H, m). m/z 472 (MH+).

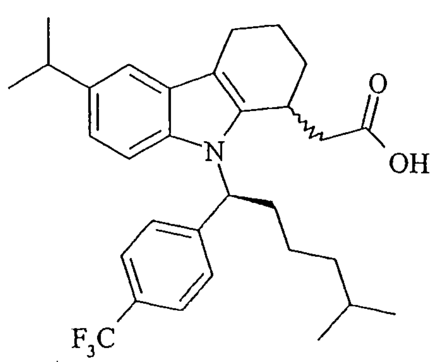
EXAMPLE 14



Prepared as described in Example 13, using cyclohexylethylmagnesium bromide in Step 1.

1H NMR δ (ppm)(500 MHz CDCl3,):7.53 (2 H, d, J = 8.2 Hz), 7.34 (1 H, s), 7.31 (2 H, d, J = 8.2 Hz), 6.87 (1 H, d, J = 8.5 Hz), 6.78 (1 H, d, J = 8.5 Hz), 5.35 (1 H, dd, J = 4.4, 10.3Hz), 3.47 (1 H, d, J = 11.4 Hz), 3.00-2.94 (1 H, m), 2.86 (1 H, dd, J = 4.2, 14.9 Hz), 2.72-2.66 (1 H, m), 2.54-2.32 (4 H, m), 2.00-1.92 (3 H, m), 1.88-1.78 (1 H, m), 1.65-1.51 (6 H, m), 1.29 (6 H, d, J = 6.9 Hz), 1.17-1.09 (5 H, m), 0.80-0.77 (2 H, m); m/z (ES+) 540 (MH+).

EXAMPLE 15

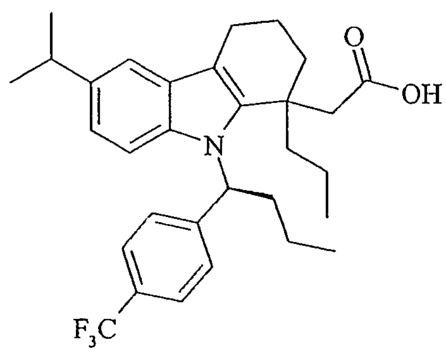


Prepared as described in Example 13, using 4-methylpentylmagnesium bromide in Step 1.

1H NMR δ (ppm)(500 MHz, CDCl3,): 7.54 (2 H, d, J = 8.1 Hz), 7.33-7.31 (3 H, m), 6.87 (1 H, dd, J = 1.3, 4.9 Hz), 6.77 (1 H, d, J = 8.4 Hz), 5.39 (1 H, dd, J = 10.6 and 3.7 Hz), 3.49 (1 H, bd, J = 6.8 Hz), 3.00-2.94 (1 H, m, J = 7.0), 2.86 (1 H, dd, J = 4.6, 15.5 Hz), 2.71-2.64 (1 H, m), 2.55-2.41 (2 H, m), 2.39-2.25 (2 H, m), 2.00-1.92 (3 H, m),1.89-1.77 (1 H, m), 1.43-1.37 (1 H, m), 1.28 (6 H, d, J = 6.9 Hz), 1.23-1.10 (4 H, m), 0.77 (3 H, d, J = 6.6 Hz), 0.71 (3 H, d, J = 6.6 Hz); m/z (ES-) 512 (MH-).

EXAMPLE 16

(6-isopropyl-1-propyl-9-{1-[4-(trifluoromethyl)phenyl]butyl}-2,3,4,9-tetrahydro-1 H -carbazol-1-yl)acetic acid



Step 1 Methyl (2-oxo-1-propylcyclohexyl)acetate

A solution of cyclohexanone (21ml, 200mmol) in THF (30ml) was added dropwise to a stirring solution of LDA (1.5M in THF, 133ml) in THF (100ml) at -78^{0}C. After stirring for 30min at -78^{0}C a solution of iodopropane (19.5ml, 200mmol) in THF (20ml) was added dropwise and stirring continued at ambient temperature for 14hrs. The reaction was quenched with HCl (2N, 100ml) and the mixture was extracted with ethyl acetate (3×100ml). The combined organic extracts were washed with brine (1×100ml), dried over $MgSO_4$ and concentrated in vacuo. The residual oil was purified by vacuum distillation (34-36^{0}C/ 10mmbar) to give 2-propylcyclohexanone as a colourless oil (2.3g, 8%).

A solution of 2-propylcyclohexanone (2.3g, 16.4mmol) in THF (10ml) was added dropwise into a stirring solution of LDA (1.5M in THF, 11ml) in THF (40ml) at -78^{0}C. After stirring for 30min at -78^{0}C, TMSCl (2.1ml, 16.4mmol) was added dropwise and stirring continued at ambient temperature for 3hrs. The reaction was

quenched with water/hexane(200ml/200ml). The organic phase was washed with saturated sodium hydrogen carbonate (1×100ml), dried over $MgSO_4$ and concentrated in vacuo. The residual oil was purified by vacuum distillation (38-45^{0}C/10mmbar) to give trimethyl[(6-propylcyclohex-1-en-1-yl)oxy]silane as a colourless oil (1.9g, 56%). A solution of potassium-t-butoxide (8.9ml, 1.0M in THF) was added dropwise to a stirring solution of this silane (1.90g, 8.9mmol) in THF (20ml) at -15^{0}C. The reaction mixture was stirred at -15^{0}C for 1hr and then cooled to -78^{0}C. Methyl bromoacetate (0.84ml, 8.9mmol) was added dropwise and stirred at -78^{0}C for 1hr and then at ambient temperature for 10hrs. The reaction mixture was quenched with water (100ml) and extracted with ethyl acetate (2×100ml). The organic extract was washed with brine (100ml), dried over $MgSO_4$ and concentrated in vacuo. The residual oil was purified by gradient flash chromatography eluting with 2% to 8% ethyl acetate in hexane to give methyl (2-oxo-1-propylcyclohexyl)acetate as a colourless oil (821mg, 43%). 1H NMR (360MHz, $CDCl_3$) δ: 3.64 (3H, s), 2.45-2.28 (2H, m), 2.01-1.12 (12H, m), 0.91-0.27 (3H, m).

<u>Step 2 Methyl (6-isopropyl-1-propyl-9-{1-[4-(trifluoromethyl)phenyl]butyl}-2,3,4,9-tetrahydro-1H-carbazol-1-yl)acetate</u>

A mixture of (2-oxo-1-propylcyclohexyl)acetate (821mg, 4.14mmol), 1-(4-isopropylphenyl)-1-{(1*S*)-1-[4-(trifluoromethyl)phenyl]butyl}hydrazine (Example 13 Step 5) (903mg, 2.58mmol) and HCl (2N, 1 drop) in ethanol (30ml) was refluxed for 18hrs. The reaction mixture was cooled to ambient temperature and concentrated. The residue was diluted with ethyl acetate (100ml) and sequentially washed with water (1× 100ml), hydrochloric acid (2N, 100ml) and brine (100ml). The organic extract was dried over $MgSO_4$ and concentrated in vacuo. The residual oil was purified by flash chromatography eluting with 2% ethyl acetate in hexane to afford the target molecule as a colourless oil of two diastereoisomers A & B (1:1) (112mg, 23%). *m/z* (ES^+) 542 (MH^+).

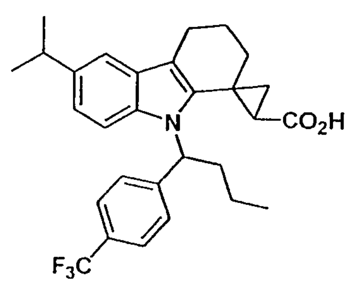
<u>Step 3</u>

The methyl ester from Step 2 was hydrolysed as described in Example 12 Step 4.

Purification by prep HPLC afforded the target compound as a mixture of two diastereoisomers A & B (1:1) (97mg, 34%) 1H NMR (400MHz, $CDCl_3$) δ: 7.53 (1H, d J = 8Hz , diast A or B), 7.47 (1H, d J = 8Hz , diast A or B), 7.40 (1H, d J = 8Hz , diast A or B), 7.33 (1H, dd J = 8Hz, 2Hz, diast A or B), 7.16-7.09 (1.5H, m, diast A+B), 6.97-6.87 (1.5H, m, diast A+B), 5.72-5.64 (1H, m, diast A+B), 5.34-5.30 (1H, br, diast A+B), 2.92-3.02 (1H, m, diast A+B),1.09-2.88 (21H, m, diast A+B), 1.02-0.83 (4.5H, m, diast A+B), 0.67-0.55 (1H, m, diast A or B) 0.11 (1.5H, t J = 8Hz, diast A or B). *m/z* (ES^+) 512 (MH+).

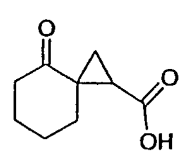
EXAMPLE 17

6-Isopropyl-9-{1-[4-trifluoromethyl)phenyl]butyl}2,3,4,9-tetrahydrospiro[carbazole-1,1'-cyclopropane]-2'-carboxylic acid



Step 1

4-Oxospiro[2,5]octane-1-carboxylic acid



1-Vinylspiro[2,5]octan-4-one (0.16g, 1.06mM) (Roberton, J. et al. Tetrahedron. 2000, 54, 8959-65) was dissolved in dichloromethane: methanol (20ml, 1:1) and cooled to -78^{0}C and ozone bubbled thorough the solution for 5 minutes. Reaction was then stirred for a further 10 minutes before quenching the reaction with dimethylsulfide (1ml) and left to warm to room temperature and stirred overnight. The reaction was evaporated and the crude aldehyde redissolved in tetrahydrofuran, (20ml)

treated with sodium chlorite (0.62g, 6.8mM) and sulfamic acid (0.25g, 2.5mM) and stirred for 3 hours at room temperature. The reaction mixture was then partitioned between ethyl acetate and water, the organic layer was washed with brine, dried over magnesium sulphate and purified on silica gel eluting with ^{i}hexane-ethyl acetate mixture to give the title compound as a mixture of isomers (0.078g) ms (ES^+) m/e 168 $[MH]^+$. ^{1}H NMR (250 MHz,$CDCl_3$) δ 9.5 (1H, br), 2.50-2.45 (1H, m), 2.32-2.20 (1H, m), 2.08-1.97 (2H, m), 1.90-1.78 (4H, m), 1.50-1.44 (1H, m), 1.35-1.10 (1H, m) and 1.04-1.01 (1H, m).

Step 2

1-(4-Isopropylphenyl)-1-{1-[4-(trifluoromethyl)phenyl]propyl}hydrazine (0.158g, 0.45mM), and 4-oxospiro[2,5]octane-1-carboxylic acid (0.076g, 0.45mM) was dissolved in ethanol (3ml) and treated with p-toluenesulphonic acid (0.154g, 0.81mM) and heated to 80^0C for 3 hours. The reaction mixture was evaporated and purified on silica gel eluting with ^{i}hexane-ethyl actetate mixture to give the product as a mixture of isomers, 0.021g, ms (ES^+) m/e 483 $[MH]^+$.